#22/Rev

Express Mail No.: EV 058 488 347 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: GATELY *et al.*

Application No.: 09/401,839

Group Art Unit: 1646

Filed: September 22, 1999

Examiner: Mertz, Prema Maria

For: PURIFICATION AND CHARACTERIZATION OF CYTOTOXIC LYMPHOCYTE MATURATION FACTOR AND MONOCLONAL ANTIBODIES THERETO

(New) Attorney Docket No.: 11126-004

REQUEST UNDER 37 C.F.R. §§ 1.607 and 1.608(b)
FOR INTERFERENCE WITH PATENT NO. 5,811,523

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §§ 1.607 and 1.608(b), Applicants request an interference between the captioned application and Trinchieri *et al.* ("Trinchieri") Patent No. 5,811,523 ("'523 patent;" Exhibit B), entitled "Antibodies to Natural Killer Stimulatory Factor," which issued September 22, 1998 from application Serial No. 956,240 ("'240 application"), filed October 22, 1997.

This Rule 608(b) Request is filed in response to the final Office Action, dated February 22, 2002,[1/] in which the Examiner denied Applicants' [Second] Request Under 37 C.F.R. §§ 1.607 And 1.608(a) For Interference With A Patent, filed July 24, 2000 ("Second Rule 608(a) Request"), and stated that Applicants must file a request under 37 C.F.R. § 1.608(b), based on the Examiner's conclusion that the effective filing date of the

---

1/ Applicants have timely filed a Notice of Appeal, dated August 22, 2002, in response to the Office Action, dated February 22, 2002. A petition for extension of time under 37 C.F.R. § 1.136(a) was filed to extend the date for response to August 22, 2002. A petition for extension of time under 37 C.F.R. § 1.136(a) from October 22, 2002 to February 22, 2003 is being filed concurrently herewith.

'523 patent was more than three months prior to the effective filing date of the captioned application for the subject matter of the proposed interference. For the reasons summarized in their Response Pursuant To 37 C.F.R. § 1.111, filed October 22, 2001, Applicants have previously shown that the effective filing date of the '523 patent is *after* the effective filing date of the captioned application for the proposed interfering subject matter of that Request. Applicants do not agree that Rule 608(b) showing is required under such circumstances and contend that the Second Rule 608(a) Request should have been sufficient to have the interference declared.

Nevertheless, in an effort to expedite the declaration of an interference, Applicants have now presented this request under Rule 608(b), *as required by the Examiner.* This Request presents several additional grounds for declaring the interference that were not presented in the prior requests under Rule 608(a). First, this Request proposes two counts (the prior requests presented a single count). Second, Applicants demonstrate that the effective filing date of their application is *prior to* the effective filing date of the Trinchieri '523 patent *for both proposed counts* and, therefore, no showing at all under Rule 608 should be necessary for declaration of an interference. Third, Applicants demonstrate that the inventions of *both proposed counts and all claims of the '523 patent are unpatentable to Trinchieri* and, therefore, Applicants are *prima facie* entitled to judgment over Trinchieri for that reason alone. Finally, Applicants respond specifically to the Examiner's comments in the Office Action, dated February 22, 2002.

Applicants expect that review of this Rule 608(b) Request will be conducted in accordance with the procedures set forth in *Basmadjian v. Landry*, 54 USPQ2d 1617 (Bd. Pat. App. & Interf. 2000). Specifically, the Examiner should review the Request to determine whether Applicants have presented evidence (see the attached exhibits, which include a previously filed declaration, and the accompanying new Declaration of Dr. William R. Benjamin) and an explanation setting forth a basis entitling the Applicants to judgment, and an Administrative Patent Judge will consider the merits of Applicants' explanation. In *Basmadjian*, the Board described the examiner's review as follows:

> the primary examiner determines, *ex parte*, whether evidence and an explanation have been filed. 37 CFR 1.608(b), last sentence. The evidence and explanation are considered by the primary examiner 'only to the extent of determining whether a basis upon which the application would be entitled to a judgment relative to the patentee is *alleged* * * *' (emphasis added). *Id.* The primary examiner is concerned only with *procedural* compliance with the requirements of

37 CFR 1.608(b). Thus, the primary examiner does not consider the sufficiency on its merits of the applicant's evidence and explanation.

54 USPQ2d at 1620 (original emphasis).[2/]

The Board described the role of the Administrative Patent Judge as follows:

> The [Administrative Patent Judge] assigned to the interference reviews the Rule 608(b) showing *on its merits* (i.e., substantively) to determine whether the applicant has established that it is *prima facie* entitled to a judgment relative to the patentee. 37 C.F.R. 1.617(a).

54 USPQ2d at 1621 (original emphasis).

To the extent the present Request is considered more appropriate under Rule 608(a),[3/] which would be considered on the merits by the Examiner, Applicants request that, upon remand from the Administrative Patent Judge, the Examiner be *required* to address (a) for *both* counts *each and every reason* presented in this Request to deny benefit of the first two parent applications from which the '523 patent claims priority and (b) *each and every basis* asserted by Applicants for unpatentability to Trinchieri of all claims of the '523 patent. To date, the Examiner has not addressed all of the previously raised bases for denying such benefit, as explained in the Response Pursuant To 37 C.F.R. § 1.111, filed October 22, 2001.

Finally, a specific response to the Office Action, dated August 22, 2002, is presented in Section XII.

IN THE CLAIMS:

Please add new claims 39-44, as follows:

39. (New) An isolated antibody which specifically reacts with cytotoxic lymphocyte maturation factor (CLMF) protein, said protein comprising:

(a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 25A-25D (SEQ ID NO:3) from amino acids 23 to 328; and

C 1

2/ See also 37 C.F.R. § 1.608(b), last sentence, which reads:

> If an examiner finds an application to be in condition for declaration of an interference, the examiner will consider the evidence and explanation only to the extent of determining whether a basis upon which the application would be entitled to a judgment relative to the patentee is alleged and, if a basis is alleged, an interference may be declared.

3/ In Section X, this Rule 608(b) Request demonstrates unpatentability to Trinchieri of all claims of the '523 patent. That is sufficient basis for declaring the requested interference under Rule 608(b). See Section IX.

(b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 26A-26C (SEQ ID NO:5) from amino acid 23 to 219.

40. (New) The isolated antibody of Claim 39 wherein the CLMF protein is capable of inducing proliferation of phytohemagglutinin (PHA)-activated peripheral blood lymphocytes.

41. (New) The isolated antibody of Claim 39 wherein said antibody reacts with said first subunit.

42. (New) The isolated antibody of Claim 39 wherein said antibody reacts with said second subunit.

C1

43. (New) An isolated antibody which specifically reacts with a subunit of cytotoxic lymphocyte maturation factor (CLMF) protein, said subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 25A-25D (SEQ ID NO:3) from amino acids 23 to 328.

44. (New) An isolated antibody which specifically reacts with a subunit of cytotoxic lymphocyte maturation factor (CLMF) protein, said subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of FIG. 26A-26C (SEQ ID NO:5) from amino acid 23 to 219.

I. BACKGROUND

A. The Parties' Applications

The Trinchieri '523 patent claims priority under 35 U.S.C. § 120 as a continuation of application Serial No. 858,000, filed May 16, 1997, which is a continuation of application Serial No. 403,013, filed March 13, 1995, which issued July 15, 1997 as United States Patent No. 5,648,467, which is a division of application Serial No. 584,941, filed September 18, 1990, which issued October 10, 1995 as United States Patent No. 5,457,038, which is a continuation-in-part of application Serial No. 307,817, filed February 7, 1989 ("'817 application;" attached as Exhibit C; abandoned), which is a continuation-in-part of application Serial No. 269,945, filed November 10, 1988 ("'945 application;" attached as Exhibit D; abandoned).

The captioned application, Serial No. 401,839, filed September 22, 1999 ("captioned application;" attached as Exhibit E) claims priority under 35 U.S.C. § 120 as a continuation of application Serial No. 08/459,151, filed June 2, 1995 ("'151 application"), which is a divisional of application Serial No. 08/205,011, filed March 2, 1994 ("'011 application;" abandoned), which is a divisional of application Serial No. 07/857,023, filed March 24, 1992 ("'023 application;" abandoned), which is a continuation-in-part of application Serial No. 07/572,284, filed August 27, 1990 ("'284 application;" attached as Exhibit F; abandoned), which is a continuation-in-part of application Serial No. 07/520,935, filed May 9, 1990 (abandoned), which is a continuation-in-part of application Serial No. 07/455,708, filed December 22, 1989 (abandoned).

As demonstrated below, for the subject matter of *both* proposed counts A and B Applicants should be accorded benefit of the filing date of their '284 application, filed August 27, 1990, and the '523 patent should, at best, be accorded benefit of the filing date of the '941 application, filed September 18, 1990.[4/] Thus, Applicants' effective filing date is *prior to* the effective filing date of the '523 patent for the subject matter of both counts A and B.

B. The Interfering Subject Matter

Applicants propose two counts, a first count directed to an antibody which specifically reacts with heterodimeric interleukin-12 ("IL-12") and a second count directed to an antibody which specifically reacts with the 30-35 kD subunit of IL-12.

IL-12 is a heterodimeric polypeptide of approximately 70 kD (kilodaltons) that is made up of two different protein subunits: a first subunit having a size of approximately 40 kD and a second subunit having a size of approximately 30-35 kD, both measured when the subunits are analyzed under reducing conditions via SDS polyacrylamide gel electrophoresis ("PAGE").

The '523 patent describes a cytokine it refers to as Natural Killer Stimulatory Factor ("NKSF"), while the captioned application describes a cytokine it refers to as Cytotoxic Lymphocyte Maturation Factor ("CLMF"). Analyses of NKSF and CLMF have

---

[4/] This statement should not be construed as an admission that Trinchieri is entitled to the benefit of *any* "parent" application of the '523 patent. As demonstrated in Section X of this Request, the claimed subject matter of the '523 patent is unpatentable to Trinchieri and, therefore, Trinchieri is not entitled to any date of invention for that subject matter.

revealed that the two cytokines are the same, except for minor amino acid differences in one of the subunits (discussed below). IL-12 has now become the preferred designation for this cytokine.

The heterodimeric IL-12 exerts multiple biological effects on certain immune cells, such as T lymphocytes and natural killer ("NK") cells. For example, IL-12 can induce synthesis of gamma interferon *in vitro* in peripheral blood lymphocytes ("PBLs"), and can also induce proliferation of phytohemagglutinin ("PHA")-activated PBLs. IL-12 can also induce proliferation in an IL-12 dependent T cell growth assay. As such, these biological effects are inherent properties of NKSF and CLMF. Neither IL-12 subunit alone exhibits such biological activities.

The subject matter of the proposed counts is unrelated to that of the prior interference between Gately and Trinchieri, Interference No. 103,184, which involved Gately application Serial No. 857,023 and Trinchieri patent application Serial No. 584,941. In that interference, there were three counts: count 2 to an isolated DNA molecule encoding the 35 kD subunit of IL-12, count 3 to an isolated DNA molecule encoding the 40 kD subunit of IL-12 and count 4 to a cell transformed with (a) a nucleic acid encoding the 35 kD subunit of IL-12 and a second nucleic acid encoding the 40 kD subunit of IL-12 or (b) a nucleic acid encoding both the 35 kD and 40 kD subunits of IL-12.

II. PROPOSED COUNT A AND DESIGNATED CLAIMS

A. Proposed Count A: Antibodies That Specifically React With Heterodimeric IL-12

Applicants propose the following count A:

PROPOSED COUNT A

An antibody which specifically reacts with a heterodimeric protein, said protein comprising:

(a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro
Gly Glu Met Val Val Leu Thr Cys Asp Thr
Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu
Asp Gln Ser Ser Glu Val Leu Gly Ser Gly

Lys Thr Leu Thr Ile Gln Val Lys Glu Phe
Gly Asp Ala Gly Gln Tyr Thr Cys His Lys
Gly Gly Glu Val Leu Ser His Ser Leu Leu
Leu Leu His Lys Lys Glu Asp Gly Ile Trp
Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu
Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu
Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys
Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu
Thr Phe Ser Val Lys Ser Ser Arg Gly Ser
Ser Asp Pro Gln Gly Val Thr Cys Gly Ala
Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala
Glu Glu Ser Leu Pro Ile Glu Val Met Val
Asp Ala Val His Lys Leu Lys Tyr Glu Asn
Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile
Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
Leu Lys Pro Leu Lys Asn Ser Arg Gln Val
Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
Phe Cys Val Gln Val Gln Gly Lys Ser Lys
Arg Glu Lys Lys Asp Arg Val Phe Thr Asp
Lys Thr Ser Ala Thr Val Ile Cys Arg Lys
Asn Ala Ser Ile Ser Val Arg Ala Gln Asp
Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp
Ala Ser Val Pro Cys Ser;

and

(b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
Gly Met Phe Pro Cys Leu His His Ser Gln
Asn Leu Leu Arg Ala Val Ser Asn Met Leu
Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
Pro Cys Thr Ser Glu Glu Ile Asp His Glu
Asp Ile Thr Lys Asp Lys Thr Ser Thr Val

Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys
Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr
Ser Phe Ile Thr Asn X Ser Cys Leu Ala
Ser Arg Lys Thr Ser Phe Met Met Ala Leu
Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys
Met Tyr Gln Val Glu Phe Lys Thr Met Asn
Ala Lys Leu Leu Met Asp Pro Lys Arg Gln
Ile Phe Leu Asp Gln Asn Met Leu Ala Val
Ile Asp Glu Leu Met Gln Ala Leu Asn Phe
Asn Ser Glu Thr Val Pro Gln Lys Ser Ser
Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
Ile Lys Leu Cys Ile Leu Leu His Ala Phe
Arg Ile Arg Ala Val Y Ile Asp Arg Val
Z Ser Tyr Leu Asn Ala Ser,

wherein X is Gly, Y is Thr and Z is Thr, or

X is Glu, Y is Tyr and Z is Met, or

X is Gly, Y is Thr and Z is Met.

1. The Recitation Of The Amino Acid Sequences Of The Two IL-12 Subunits In Proposed Count A Is Proper

During prosecution of the '523 patent, the Examiner *required* that all claims recite the complete amino acid sequences of the two "NKSF" subunits or, where only one subunit was identified in the claim, the complete amino acid sequence of that subunit. For the convenience of the Examiner, a copy of the file history of the '523 patent is attached as Exhibit G. As originally filed in the Preliminary Amendment, dated October 22, 1997, none of Trinchieri's antibody claims recited any amino acid sequence for either subunit of NKSF. In the first Office Action, dated March 2, 1998, the Examiner rejected all claims under 35 U.S.C. § 112, first paragraph, on grounds that the specification was not enabling for antibodies to proteins other than the heterodimeric protein having the amino acid sequences listed in the figures of the application for each of its two subunits, or the individual subunits of the heterodimer having those amino acid sequences. The Examiner determined that the complete amino acid sequences must be added to limit the claim to the enabled subject matter. In response, Trinchieri amended the claims to recite the complete amino acid sequences disclosed for each subunit. See Amendment, dated March 23, 1998, in the '240 application that issued as the '523 patent. A Notice of Allowance followed that amendment.

Thus, recitation of the complete amino acid sequence of each subunit recited in a claim was material to patentability of Trinchieri's claims because *without those limitations the claims would not have issued.* Consistent with this prosecution history, Applicants have presented proposed count A which recites the amino acid sequences of both subunits.

2. Discussion Of The Sequences Recited In Proposed Count A

The amino acid sequence of the 40 kD protein subunit recited in part (a) of proposed count A is *identical* to the sequence depicted in Fig. 1 of the '523 patent from amino acids 23 to 328, as recited in part (a) of claim 1 of the '523 patent. This amino acid sequence is *identical* to the sequence depicted in Figs. 25A-25D of the captioned application from amino acids 23-328, as recited in part (a) of claim 33 of the captioned application.

With respect to the 30-35 kD subunit recited in part (b) of proposed count A, first consider the sequence of amino acids 23-219 of Fig. 26 of the captioned application, which describes the mature form of the 30-35 kD subunit. The residues of interest have the following amino acids at the noted positions: position 108 (Gly), position 208 (Thr) and position 213 (Thr). This sequence corresponds to part (b) of the proposed count where X is Gly, Y is Thr and Z is Thr.

Second, consider the two sequences of positions 57-253 of Fig. 2 of the '523 patent, which describe the mature form of the 30-35 kD subunit. The *amino acid sequence* recited in Fig. 2 indicates the following amino acids at the noted positions: position 142 (Glu), position 242 (Tyr) and position 247 (Met). This sequence corresponds to part (b) of the proposed count where X is Glu, Y is Tyr and Z is Met. The *nucleotide sequence* recited in Fig. 2 *encodes* the following amino acids at the noted positions: position 142 (GGG = Gly), position 242 (ACT = Thr) and position 247 (ATG = Met). This sequence corresponds to part (b) of the proposed count where X is Gly, Y is Thr and Z is Met.

The positions 142, 242 and 247 of Fig. 2 of the '523 patent correspond to positions 108, 208 and 213, respectively, of Fig. 26 of the captioned application.

The following summarizes the amino acids at these positions:

Captioned Application		'523 Patent		
Position	**Amino Acid Sequence**	**Position**	**Amino Acid Sequence**	**Nucleotide Sequence**
X 108	Gly	**X 142**	Glu	Gly
Y 208	Thr	**Y 242**	Tyr	Thr
Z 213	Thr	**Z 247**	Met	Met

Thus, the 30-35 kD subunit *recited in the amino acid sequence* of Fig. 2 of the '523 patent and the corresponding subunit of Applicants' claims differ at the *three* positions noted in the table above. *The 30-35 kD subunit encoded by the nucleotide sequence of Fig. 2 of the '523 patent differs from the corresponding subunit of Applicants' claims at the one position (247/213) noted in the table above.* Finally, the two sequences for the 30-35 kD subunit found in the '523 patent differ from each other at the *two* positions (142/108 and 242/208) noted in the table above.

Proposed count A is broad enough to encompass any *antibody* that specifically reacts with IL-12 having the recited subunits, where the 40 kD subunit has the mature amino acid sequence in Fig. 25 of the captioned application, which is identical to the mature amino acid sequence in Fig. 1 of the '523 patent *and recited in claim 1 of the '523 patent*, and the 30-35 kD subunit has either (a) the mature amino acid sequence in Fig. 26 of the captioned application *or* (b) the mature amino acid sequence depicted in Fig. 2 *and recited in claim 1* of the '523 patent *or* (c) mature amino acid sequence encoded by the nucleotide sequence depicted in Fig. 2 of the '523 patent. This is appropriate, since, at the time an interference is initially declared, a count shall not be narrower in scope than any claim designated to correspond to the count. 37 C.F.R. § 1.606.

3. Proposed Count A Does Not Recite Any Specific Biological Activity Of IL-12 Because The Biological Activity Of The IL-12 Antigen Is Not Relevant To Identifying The Antibody

The biological activity of the IL-12 antigen, *i.e.*, the molecule to which the antibody specifically reacts, is not relevant to identifying the antibody. While a biological activity is a property of the protein, IL-12 has many biological activities, and many of these individually are properties of other proteins as well. So recitation of just one biological activity ("capable of inducing the production of gamma interferon in vitro in human peripheral blood lymphocytes," as in claim 1 of the '523 patent) does not distinguish the

protein antigen over other proteins. Here, proposed count A recites the complete amino acid sequence of both IL-12 subunits, thus fully defining the IL-12 antigen in the context of this antibody invention. Note also that claims 6 and 7 of the '523 patent do not recite any biological activity for the respective subunits against which those claimed antibodies react, yet the subunits are fully described by their complete amino acid sequences, which the Examiner deemed sufficient to issue the claims.

Consequently, proposed count A does not recite any specific biological activity for IL-12 because it is not necessary to define the antibodies claimed, given that the complete amino acid sequence of each subunit is recited.

Nevertheless, Applicants discuss for the record that the biological activity of the heterodimeric protein (NKSF) recited in claim 1 of the '523 patent is an inherent property of Applicants' heterodimeric protein (CLMF) as well.

The ability of NKSF (*i.e.*, IL-12) to induce production of gamma interferon *in vitro* in human peripheral blood lymphocytes ("PBLs") is explicitly recited in claim 1 of the '523 patent and discussed in the specification ('523 patent, col. 2, ll. 34-54; col. 4, lines 45-47 and col. 20, ll. 13-36). In addition, the '523 patent teaches that NKSF induces proliferation of phytohemagglutinin (PHA)-activated PBLs ('523 patent, col. 21, ll. 34-54), but that activity is not recited in the claim 1. NKSF can also induce proliferation in an NKSF dependent T cell growth assay. All of these biological activities are inherent properties of the NSKF protein. See ¶ 10, Declaration of William R. Benjamin ("Benjamin Declaration"), filed concurrently herewith.[5/]

The ability of CLMF (*i.e.*, IL-12) to induce proliferation of phytohemagglutinin (PHA)-activated PBLs is described in the captioned application (captioned application, p. 19, l. 15 to p. 20, l. 12) and in Example 9 (pp. 54-60). The activity of inducing synthesis of gamma interferon *in vitro* in human peripheral blood lymphocytes ("PBLs") is not described in the captioned application, but CLMF clearly exhibits that biological activity as well (Benjamin Dec., ¶ 10). Both activities are inherent properties of CLMF (Benjamin Dec., ¶ 10).

[5/] Dr. Benjamin's qualifications as an expert are found in his declaration at ¶¶ 1-7.

4. Proposed Count A Does Not Recite The Degree Of Purity Of IL-12 Antigen Because It Is Not Relevant To Identifying The Antibody

The *purity* of the IL-12 antigen, *i.e.*, the antigen with which the claimed antibody specifically reacts, is not relevant to identifying the antibody (Benjamin Dec., ¶ 12). An antibody that specifically reacts with an antigen would do so whether the antigen is "substantially free from association with other proteinaceous materials" (as recited in claim 1 of the '523 patent) or is present in mixture with proteinaceous materials (Benjamin Dec., ¶ 12). Thus, the recitation that the antibody specifically reacts with IL-12 that is "substantially free from association with other proteinaceous materials" does not distinguish the claimed antibodies from any antibody that specifically reacts with IL-12 of any purity. Here, proposed count A recites the complete amino acid sequence of both IL-12 subunits, thus fully defining the IL-12 antigen in the context of this antibody invention. Note also that claims 6 and 7 of the '523 patent do not recite any degree of purity for the respective subunits against which those claimed antibodies react, yet the subunits are fully descried by their complete amino acid sequences, which the Examiner deemed sufficient to issue the claims.

Consequently, proposed count A does not recite that the IL-12 antigen is "substantially free from association with other proteinaceous materials" because that limitation is not necessary to define the antibodies claimed, given that the complete amino acid sequence of each subunit is recited.

B. Claims 1, 2 And 4-6 Of The '523 Patent Should Be Designated To Correspond To Proposed Count A

Applicants propose that claims 1, 2 and 4-6 of the '523 patent be designated as corresponding to proposed count A. The claims do not correspond exactly to proposed count A, but are directed to the same patentable invention as proposed count A. 37 C.F.R. § 1.601(n).

Claim 1 is directed to an "antibody" which specifically reacts with NKSF, where NKSF "is capable of inducing the production of gamma interferon *in vitro* in human peripheral blood lymphocytes," "is substantially free from association with other proteinaceous materials" and comprises the two subunits having the specific mature amino acid sequences disclosed in Figs. 1 and 2 of the '523 patent. As noted above, the recited *inherent* biological activity does not distinguish NKSF from other proteins having that activity; rather, the recitation of the complete amino acid sequences of the protein distinguishes it from all others. Nor does the degree of purity of the IL-12 with which the antibodies specifically react distinguish those antibodies from antibodies that react with IL-12

of any purity. Therefore, while proposed count A does not recite the biological activity and degree of purity limitations recited in claim 1, both are nonetheless directed to the same patentable invention because the recitations of the biological activity and degree of purity of the IL-12 do not define a separate patentable invention. *In re Ruschig*, 343 F.2d 965, 973, n.8, 145 USPQ 274, 286 n.8 (C.C.P.A. 1965) (stating that "attorneys often write compound claims including a statement of some *inherent* property, general or specific," and that "[w]here the balance of the claim fully identifies the compound . . . and the property is inherent, we fail to see that such statements add anything to the claim definition of the named compound.").

The heterodimeric protein recited in claim 1 is *identical* to one of the three proteins recited in proposed count A (where X is Glu, Y is Tyr and Z is Met) and, therefore, an antibody (polyclonal or monoclonal)[6/] which specifically reacts with the protein recited in claim 1 is not separately patentable from an antibody of proposed count A and should be designated to correspond to proposed count A. Moreover, there are only one, two or three specific amino acids that differ among the three 30-35 kD subunits recited in proposed count A. The 40 kD subunits are *identical*. For a perspective of these differences, it is noted that the entire mature 30-35 kD subunit has a total of 197 amino acids and the mature 40 kD subunit has a total of 306 amino acids. IL-12 comprises these two subunits.

Dependent claim 2 and independent claim 6 recite an antibody which specifically reacts with the 40 kD subunit. As the 40 kD subunit recited in claims 2 and 6 is *identical* to the 40 kD subunit recited in proposed count A, the antibodies recited in claims 2 and 6 and proposed count A are directed to the identical invention and those claims should be designated as corresponding to proposed count A. Also, as discussed in Section II.C.1 (discussing support for Applicants' claim 35), data in Applicants' application shows that antibodies generated upon immunization with a partially purified IL-12 preparation bound specifically to the 75 kD heterodimer *and* free 40 kD subunit. See the captioned application, p. 73, l. 20 to p. 74, l .9.

6/ A "polyclonal antibody" is a mixture of antibody molecules directed to numerous antigens and to any number of epitopes on a particular antigen. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368-69, 231 USPQ 81, 82 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). A monoclonal antibody, on the other hand, is directed to a single epitope. *Id.* A claim to an "antibody" is generic to (a) the subgenus of polyclonal antibodies that specifically react with IL-12 and (b) the subgenus of monoclonal antibodies that specifically react with IL-12.

Dependent claims 4 and 5 depend from claim 1 and specify that the antibody is a murine or a human antibody, respectively. It is well known that antibodies are produced by mammals, including mice and humans. Given the antibodies having the properties recited in proposed count A, it would have been obvious to produce such antibodies in mice or humans. Thus, claims 4 and 5 define the same patentable invention as proposed count A. Accordingly, claims 4 and 5 should be designated as corresponding to proposed count A.

C. Claims 33-35, 37, 39-41 And 43 Of The Captioned Application Should Be Designated To Correspond To Proposed Count A

Applicants' claims 33-35, 37, 39-41 and 43 of the captioned application do not correspond exactly to proposed count A, but these claims should be designated as corresponding to proposed count A because they are directed to the same patentable invention. 37 C.F.R. § 1.601(n). The pending claims are listed in Exhibit A.

1. New Claims 33-35, 37, 39-41 And 43 Are Supported In Applicants' Specification

Claims 33-35, 37, 39-41 and 43 are fully supported in the specification of the captioned application as discussed below. Claims 33-35 and 37 have been pending as early as July 24, 2000, and have been found acceptable under 35 U.S.C. § 112.

Claims 33 and 34 are directed to a monoclonal antibody which specifically reacts with CLMF protein, said CLMF protein comprising a subunit of 40 kD under reducing conditions comprising the amino acid sequence of captioned application Figs. 25A-25D (SEQ ID NO:3) from amino acid residues 23 to 328. This sequence of the 40kD subunit is *identical* to the sequence of the 40 kD subunit recited in part (a) of proposed count A. The CLMF protein of claim 33 also comprises a subunit of 30-35 kD under reducing conditions comprising the amino acid sequence of captioned application Figs. 26A-26C (SEQ ID NO:5) from amino acid residues 23 to 219. This sequence of the 30-35kD subunit is *identical* to one of the three sequences (where X is Gly, Y is Thr and Z is Thr) recited for the 30-35 kD subunit recited in part (b) of proposed count A. Claim 34, which depends from claim 33, recites one of the biological activities of the CLMF protein, in particular, that the CLMF protein can induce proliferation of phytohemagglutinin (PHA)-activated peripheral blood cells.

These claims are fully supported by the captioned application. Example 13 (pp. 71-78) describes the successful generation and characterization of monoclonal antibodies directed against CLMF. The rats were immunized with partially purified CLMF (p. 71, ll. 7-10). At p. 72, ll. 18-26, the specification states:

> Four individual monoclonal antibodies also immunoprecipitated the 75 kDa heterodimer and the free 40 kDa subunit (Fig. 28) but did not immunoprecipitate the 92 kDa or 25 kDa labelled proteins [which were contaminants in the CLMF preparation]. The immunoprecipitation assay identified twenty hybridomas which secreted anti-CLMF antibodies (Table 14). All the antibodies immunoprecipitated the radiolabeled 75 kDa heterodimer and the free 40 kDa subunit as determined by SDS/PAGE and autoradiography (data shown for 4 representative antibodies in Fig. 28).

The structural features of the CLMF protein recited in the claims are as characterized and described in the captioned application. For a characterization of the size and amino acid sequence of the two CLMF subunits, see, *e.g.*, p. 33, ll. 10-14 and Fig. 7; p. 64, ll. 10-17 and Figs. 25A-25D; and p. 67, ll. 5-9 and Figs. 26A-26C. With respect to the biological activity of the CLMF heterodimer, the ability of the heterodimer to induce proliferation of PHA-activated peripheral blood cells (referred to in the specification as a "T cell growth factor (TGF) assay") is described and demonstrated at p. 19, l. 15 to p. 21, l. 2, and in Example 9 (pp. 54-60).

Claim 35, which depends from claim 33, and independent claim 37 are directed to monoclonal antibodies that specifically react with the 40 kD CLMF subunit. Example 13 describes the production and characterization of monoclonal antibodies which specifically react with the 40 kD CLMF subunit. See especially p. 73, l. 20 to p. 74, l. 9, where the Applicants report that all of the monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9).

Claims 39-41 and 43 are identical to claims 33-35 and 37, respectively, except that claims 39-41 and 43 are directed to "isolated antibodies" while claims 33-35 and 37 are directed to "monoclonal antibodies." Because the specification describes and enables the monoclonal antibody claims (as described immediately above), and corresponding polyclonal antibodies are made as an early part of preparing the monoclonal antibodies, claims 39-41 and 43 are also supported in the captioned application. See, for example, p. 71, l. 33 to p. 72, l. 3. The term "isolated" distinguishes over any naturally occurring antibodies otherwise meeting the claim limitations. Applicants' isolation of serum from immunized animals with IL-12 is one example of an isolated antibody supporting this limitation. See, for example, p. 71, ll. 33-35.

As noted above, Example 13 describes the production of monoclonal antibodies that specifically react with CLMF. One step in producing monoclonal antibodies is to prepare polyclonal antibodies that specifically react with CLMF. The polyclonal antibodies were obtained from rats immunized as described at p. 71, ll. 7-15 and according to the immunization schedule of Table 13. The properties of the polyclonal antibodies are described at p. 71, l. 33 to p. 72, l. 3 and Fig. 27:

> Serum isolated at the 3rd bleed from the rat immunized with partially purified CLMF (Table 13) neutralized CLMF bioactivity (5 units/ml) as determined in the TGF assay (Fig. 27). This neutralization could be blocked by adding excess CLMF (200 units/ml) demonstrating that the neutralization by the antiserum was specific for CLMF (Fig. 27). Normal rat serum did not neutralize CLMF bioactivity (Fig. 27).

The isolated serum is an example of an antibody of claim 39 that specifically reacts with CLMF.

2. Explanation Why Claims 33-35, 37, 39-41 And 42 Correspond To Proposed Count A

Claims 33-35, 37, 39-41 and 42 do not correspond exactly to proposed count A, but these claims should be designated as corresponding to proposed count A because they are directed to the same patentable invention. 37 C.F.R. § 1.601(n).

Each of Applicants' claims 33-35 and 37 is directed to a monoclonal antibody which specifically reacts with heterodimeric CLMF protein or its 40 kD subunit. Proposed count A recites an antibody which specifically reacts with one of three heterodimeric IL-12 proteins, one of which is *identical* to the CLMF of Applicants' claim 33 (where X is Gly, Y is Thr and Z is Thr), so the monoclonal antibody of claim 33 would be the same patentable invention as the antibodies of proposed count A. Additionally, the 40 kD subunit of all three of the heterodimeric IL-12 proteins recited in proposed count A are *identical* to the 40 kD subunit of claim 33. The 30-35 kD subunit recited in claim 33 is *identical* to one of the 30-35 kD subunits recited in proposed count A and differs from the other two 30-35 kD subunits recited in proposed count A by one, two or three specific amino acids, as noted above. It is well known that an antibody can be of either monoclonal or polyclonal origin. As such, monoclonal antibodies which specifically react with a particular antigen (in this case heterodimeric IL-12) are species of all antibodies that specifically react with the antigen and are not separately patentable from polyclonal antibodies that specifically react with the same antigen. Therefore, claim 33 is directed to the same patentable invention as proposed count A and should be designated as corresponding to proposed count A.

Claim 34 adds that the CLMF protein is capable of inducing proliferation of phytohemagglutinin-activated peripheral blood lymphocytes, an inherent property of the heterodimer having the amino acid sequences recited in claim 33 (Benjamin Dec., ¶ 10). Although proposed count A does not recite any biological activity for the heterodimeric protein, the heterodimeric CLMF protein of claims 33 and 34 is identical to one of the proteins recited in proposed count A and exhibits the same activity as that same protein recited in proposed count A. The captioned application demonstrates that CLMF induces proliferation of PHA-activated PBLs (Example 9, pp. 54-60), as recited in claim 34. Thus, claim 34 should be designated as corresponding to proposed count A.

Claim 35, which depends from claim 33, and independent claim 37 are directed to monoclonal antibodies that specifically react with the 40 kD CLMF subunit. Example 13 describes the production and characterization of monoclonal antibodies which specifically react with the 40 kD CLMF subunit. See especially p. 73, l. 20 to p. 74, l. 9, where the Applicants report that all of the monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9). Thus, claims 35 and 37 are directed to the same patentable invention as proposed count A.

As noted, claims 39-41 and 43 are identical to claims 33-35 and 37, respectively, except that claims 39-41 and 43 are directed to "isolated antibodies" while claims 33-35 and 37 are directed to "monoclonal antibodies." For all the reasons stated above that claims 33-35 and 37 are directed to the same patentable invention as proposed count A, so too are claims 39-41 and 43 directed to the same patentable invention as proposed count A. The monoclonal nature of the antibodies of claim 33-35 and 37 does not make them a separate patentable invention from the polyclonal antibodies of proposed count A, since given the polyclonal antibodies of proposed count A it would have been obvious to make the monoclonal antibodies of claims 39-41 and 43.

III. PROPOSED COUNT B AND DESIGNATED CLAIMS

A. Proposed Count B: Antibodies That Specifically React With The 30-35 kD Subunit

Applicants propose the following count B:

PROPOSED COUNT B

An antibody which specifically reacts with a 30-35 kD protein, said protein having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
Gly Met Phe Pro Cys Leu His His Ser Gln
Asn Leu Leu Arg Ala Val Ser Asn Met Leu
Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
Pro Cys Thr Ser Glu Glu Ile Asp His Glu
Asp Ile Thr Lys Asp Lys Thr Ser Thr Val
Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys
Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr
Ser Phe Ile Thr Asn X Ser Cys Leu Ala
Ser Arg Lys Thr Ser Phe Met Met Ala Leu
Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys
Met Tyr Gln Val Glu Phe Lys Thr Met Asn
Ala Lys Leu Leu Met Asp Pro Lys Arg Gln
Ile Phe Leu Asp Gln Asn Met Leu Ala Val
Ile Asp Glu Leu Met Gln Ala Leu Asn Phe
Asn Ser Glu Thr Val Pro Gln Lys Ser Ser
Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
Ile Lys Leu Cys Ile Leu Leu His Ala Phe
Arg Ile Arg Ala Val Y Ile Asp Arg Val
Z Ser Tyr Leu Asn Ala Ser,

wherein X is Gly, Y is Thr and Z is Thr, or

X is Glu, Y is Tyr and Z is Met, or

X is Gly, Y is Thr and Z is Met.

The amino acid sequence of the 30-35 kD subunit recited in proposed count B is identical to the sequence recited in part (b) of proposed count A. The basis for this

sequence is discussed in Section II.A.2. As noted in that section, during prosecution of the '523 patent the Examiner required that the claims to antibodies that specifically react with the 30-35 kD subunit recite the amino acid sequence of that subunit. Consequently, Applicants have recited that sequence in proposed count B.

B. Proposed Count B Is Directed To A Separately Patentable Invention From Proposed Count A

Proposed count B is directed to antibodies that specifically react with the 30-35 kD subunit of IL-12 and proposed count A is directed to an antibody that specifically reacts with heterodimeric IL-12. As shown in this section, those two proposed counts are directed to separately patentable inventions.

As developed more fully below, only by using special techniques was it possible for Applicants to generate the antibodies of proposed count B that specifically react with the 30-35 kD subunit (Example 14, pp. 79-80). One of ordinary skill in the art would not have known, given antibodies that specifically react with heterodimeric IL-12 (of proposed count A), how to make antibodies that specifically react with the 30-35 kD subunit (of proposed count B). Thus, the antibodies of proposed count B are separately patentable over the antibodies of proposed count A.

The data in Applicants' specification (p. 73, l. 20 to p. 74, l. 9) demonstrates that all of the 20 monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9). Since none of those antibodies specifically bound to the 30-35 kD subunit, antibodies to the 30-35 kD subunit would not have been obvious, even assuming antibodies to the 75 kD heterodimer and the 40 kD subunit were in the prior art.

The data of Applicants' specification is consistent with the conclusions of Applicants' expert, David H. Presky, Ph.D.[7/] See the Second Declaration of Dr. David H. Presky, filed July 24, 2000 ("Second Presky Declaration;" attached as Exhibit H). Making antibodies, especially monoclonal antibodies, which specifically bind the NKSF 30-35 kD subunit is difficult, and clearly not routine, when using purified NKSF or reconstituted NKSF heterodimer as the antigen (Second Presky Dec., ¶ 7). This fact is illustrated by the results

---

7/ Dr. Presky's qualifications as an expert are found in his declaration, ¶¶ 1-5.

reported in D'Andrea *et al.*[8] and in Chizzonite *et al.*,[9] a scientific paper co-authored in 1991 by a subset of the Applicants of the captioned application.

Both D'Andrea *et al.* and Chizzonite *et al.* concern generation of antibodies directed against IL-12 (*i.e.*, NKSF or CLMF) and both of these publications point out the difficulties associated with attempting to produce antibodies which specifically bind to the NKSF 30-35 kD subunit when a purified sample of NKSF heterodimer is used as the starting antigen. The results in D'Andrea *et al.* show that antibodies generated against recombinantly produced NKSF heterodimer (referred to in D'Andrea *et al.* as "C11" antibodies) fail to react with the 30-35 kD NKSF subunit and exhibit a reactivity pattern similar to antibodies generated against just the NKSF 40 kD subunit (referred to in D'Andrea *et al.* as the "C8 series" of antibodies), *i.e.*, only react with the 40 kD subunit (D'Andrea *et al.*, p. 1390, left column, and Fig. 1).

Chizzonite *et al.* reports on monoclonal and polyclonal antibodies directed against IL-12 (NKSF or CLMF) generated using purified or partially purified NKSF heterodimer (Benjamin Dec., ¶ 14). The results presented in Chizzonite *et al.* demonstrate that using purified NKSF resulted only in the generating of antibodies which specifically bind the 40 kD subunit (Chizzonite *et al.*, p. 1554, left column). See Benjamin Dec., ¶ 14. That is, no antibodies were produced which specifically react with the 30-35 kD subunit (Benjamin Dec., ¶ 14). In attempting to explain the reason for the apparent preference for antibodies directed against the 40 kD subunit, Chizzonite *et al.* points out that significant amounts of the free 40 kD subunit are present in purified IL-12 samples, which can bias toward identification of antibodies against the 40 kD subunit (Chizzonite *et al.*, p. 1555, left column). See Benjamin Dec., ¶ 14. Chizzonite *et al.* also reports that, apparently, antibodies against the 30-35 kD subunit arise "only after multiple immunizations," as opposed to antibodies against the 40 kD subunit, which arise very rapidly (Chizzonite *et al.*, p. 1555, left column). See Benjamin Dec., ¶ 14.

---

[8] D'Andrea *et al.*, 1992, "Production of Natural Killer Cell Stimulatory Factor (Interleukin 12) by Peripheral Blood Mononuclear Cells," J. Exp. Med. 176: 1387-1398 (attached as Exhibit I).

[9] Chizzonite *et al.*, 1991, "IL-12: Monoclonal Antibodies Specific for the 40 kDa Subunit Block Receptor Binding and Biologic Activity of Activated Human Lymphoblasts," J. Immunol. 147: 1548-1556 (attached as Exhibit J).

The techniques required by Chizzonite *et al.* to generate antibodies against the 30-35 kD subunit are not standard techniques that would have been utilized by one of skill in the art (Benjamin Dec., ¶ 15). Rather, using standard techniques, one skilled in the art, upon observing that immunized animals produced a sufficient titer of polyclonal antibodies that specifically react with IL-12, would have terminated the immunization schedule and sacrificed the animal (Benjamin Dec., ¶ 15). Thus, using standard techniques, further multiple immunizations would not have been done and antibodies specific for the 30-35 kD subunit would not have been made (Benjamin Dec., ¶ 15).

Clearly, then, the results presented in both D'Andrea *et al.* and Chizzonite *et al.* demonstrate that when "standard" methods, such as using purified NKSF antigen, are employed to produce antibodies that recognize the 40 kD subunit as well as antibodies that recognize the 30-35 kD subunit, such methods fail to yield antibodies that specifically react with the 30-35 kD subunit.

Moreover, in order to make antibodies that specifically bind to the 30-35 kD subunit, Applicant first cloned the DNA encoding that subunit and from the DNA sequence of that clone selected an 11-amino acid sequence within the encoded mature protein to use as an immunogen to raise antibodies (p. 79, ll. 6-8). That 11-amino acid sequence was chemically synthesized and conjugated to keyhole limpet hemocyanin and the conjugate was used to immunize rabbits (p. 79, ll. 8-15). Serum from the rabbits contained antibodies that specifically react with the 30-35 kD subunit and also reacted with IL-12 (p. 79, ll. 1-10). However, sufficient amino acid sequence information for the 30-35 kD subunit of IL-12 was not available in the art in 1990.

Thus, given antibodies that specifically react with IL-12 and the 40 kD subunit of proposed count A, which were generated from immunization with partially pure CLMF, one of ordinary skill in the art would not have found it obvious how to make antibodies that specifically react with the 30-35 kD subunit, which Applicants could only generate from immunization with a synthetic peptide having a specific amino acid sequence of the 30-35 kD subunit.

Therefore, the subject matter of proposed count B is separately patentable from the subject matter of proposed count A and an interference should be declared with Applicants' two proposed counts.

C. Claims 3 And 7 Of The '523 Patent Should Be Designated To Correspond To Proposed Count B

Applicants propose that claims 3 and 7 of the '523 patent be designated as corresponding to proposed count B. The claims do not correspond exactly to proposed count B, but they are directed to the same patentable invention. 37 C.F.R. § 1.601(n).

Dependent claim 3 and independent claim 7 recite an antibody which specifically reacts with the 30-35 kD subunit. The 30-35 kD subunit recited in claims 3 and 7 is *identical* to one of the three 30-35 kD subunits recited in proposed count B and, therefore, antibodies which specifically react with the 30-35 kD subunit recited in claims 3 and 7 are the same patentable invention as antibodies which specifically react with the 30-35 kD subunit of proposed count B. In addition, the 30-35 kD subunit of claims 3 and 7 differs from the other two subunits recited in proposed count B by one, two or three specific amino acid out of a total of 197 amino acids, as discussed above. Therefore, claims 3 and 7 should be designated as corresponding to proposed count B.

D. Claims 36, 38, 42 And 44 Of The Captioned Application Should Be Designated To Correspond To Proposed Count B

Applicants' claims 36, 38, 42 and 44 of the captioned application do not correspond exactly to proposed count B, but these claims should be designated as corresponding to proposed count B because all are directed to the same patentable invention. 37 C.F.R. § 1.601(n). The pending claims are listed in Exhibit A.

1. Claims 36, 38, 42 And 44 Are Supported In Applicants' Specification

Claims 36, 38, 42 and 44 are fully supported in the specification of the captioned application. Claims 36 and 38 have been pending as early as July 24, 2000, and have been found acceptable under 35 U.S.C. § 112.

Claim 36, which depends from claim 33, and independent claim 38 are directed to monoclonal antibodies that react with the 30-35 kD CLMF subunit. Example 14 (pp. 79-80) describes a method for producing monoclonal antibodies which specifically react with the 35 kD CLMF subunit, wherein the monoclonal antibodies are generated against a synthetic peptide containing a 35 kD CLMF subunit amino acid sequence.

As noted above, the only difference between claims 36 and 38 and claims 42 and 44, respectively, is that claims 36 and 38 are directed to "isolated antibodies" and claims 42 and 44 are directed to "monoclonal antibodies." Since polyclonal antibodies must be made as one step in the preparation of monoclonal antibodies, the support noted for claims 36

and 38 equally supports claims 42 and 44. The term "isolated" distinguishes over any naturally occurring antibodies otherwise meeting the claim limitations. Applicants' isolation of serum from animals immunized with IL-12 is one example of an isolated antibody supporting this limitation. See, for example, p. 71, ll. 33-35.

2. Explanation Why Claims 36, 38, 42 And 44 Correspond To Proposed Count B

Claims 36 and 38 do not correspond exactly to proposed count B, but they should be designated as corresponding to proposed count B because each is directed to the same patentable invention. 37 C.F.R. § 1.601(n).

Claim 36, which depends from claim 33, and independent claim 38, recite a monoclonal antibody which specifically reacts with the 30-35 kD CLMF subunit. As discussed above, the 30-35 kD CLMF subunit is identical to one of the three 30-35 kD subunits recited in the proposed count and differs by one, two or three specific amino acids from the other two 30-35 kD subunits recited in the proposed count. The monoclonal antibodies recited in claims 36 and 37, therefore, are not separately patentable from antibodies which specifically react with the 30-35 kD subunits recited in proposed count B. As such, claims 36 and 37 are directed to the same patentable invention as the proposed count and should be designated as corresponding to proposed count B.

For the reasons discussed above, the monoclonal nature of the antibodies of claims 42 and 44, the only difference between those claims and claims 36 and 38, does not define an invention separately patentable from those claims or proposed count B.

IV. PROPOSED COUNTS A AND B ARE DIRECTED TO INVENTIONS THAT ARE SEPARATELY PATENTABLE FROM THE INVENTION OF PROPOSED COUNT C IN APPLICANTS' COPENDING APPLICATION

In their copending application Serial No. 10/267,565, filed October 8, 2002, Applicants have requested an interference with Trinchieri Patent No. 6,300,478 (attached as Exhibit K), entitled "Antibodies to Natural Killer Stimulatory Factor," which issued October 9, 2001. For the Examiner's convenience, a copy of that Request Under 37 C.F.R. §§ 1.607 and 1.608(a) For Interference With Patent No. 6,300,478, filed January 23, 2003 (without exhibits), is attached as Exhibit L.

A. **Proposed Count C: Antibodies That Specifically React With Heterodimeric IL-12 And Block A Biological Activity Of IL-12**

In that request for interference, Applicants presented the following proposed count C:

PROPOSED COUNT C

An isolated antibody which specifically reacts with a heterodimeric protein, said protein comprising:

(a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro
Gly Glu Met Val Val Leu Thr Cys Asp Thr
Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu
Asp Gln Ser Ser Glu Val Leu Gly Ser Gly
Lys Thr Leu Thr Ile Gln Val Lys Glu Phe
Gly Asp Ala Gly Gln Tyr Thr Cys His Lys
Gly Gly Glu Val Leu Ser His Ser Leu Leu
Leu Leu His Lys Lys Glu Asp Gly Ile Trp
Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu
Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu
Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys
Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu
Thr Phe Ser Val Lys Ser Ser Arg Gly Ser
Ser Asp Pro Gln Gly Val Thr Cys Gly Ala
Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala
Glu Glu Ser Leu Pro Ile Glu Val Met Val
Asp Ala Val His Lys Leu Lys Tyr Glu Asn
Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile
Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
Leu Lys Pro Leu Lys Asn Ser Arg Gln Val
Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
Phe Cys Val Gln Val Gln Gly Lys Ser Lys

Arg Glu Lys Lys Asp Arg Val Phe Thr Asp
Lys Thr Ser Ala Thr Val Ile Cys Arg Lys
Asn Ala Ser Ile Ser Val Arg Ala Gln Asp
Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp
Ala Ser Val Pro Cys Ser;

and

(b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the following amino acid sequence:

Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
Gly Met Phe Pro Cys Leu His His Ser Gln
Asn Leu Leu Arg Ala Val Ser Asn Met Leu
Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
Pro Cys Thr Ser Glu Glu Ile Asp His Glu
Asp Ile Thr Lys Asp Lys Thr Ser Thr Val
Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys
Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr
Ser Phe Ile Thr Asn X Ser Cys Leu Ala
Ser Arg Lys Thr Ser Phe Met Met Ala Leu
Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys
Met Tyr Gln Val Glu Phe Lys Thr Met Asn
Ala Lys Leu Leu Met Asp Pro Lys Arg Gln
Ile Phe Leu Asp Gln Asn Met Leu Ala Val
Ile Asp Glu Leu Met Gln Ala Leu Asn Phe
Asn Ser Glu Thr Val Pro Gln Lys Ser Ser
Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
Ile Lys Leu Cys Ile Leu Leu His Ala Phe
Arg Ile Arg Ala Val Y Ile Asp Arg Val
Z Ser Tyr Leu Asn Ala Ser,

wherein X is Gly, Y is Thr and Z is Thr, or

X is Glu, Y is Tyr and Z is Met, or

X is Gly, Y is Thr and Z is Met,

and wherein said antibody is capable of blocking a biological activity of said protein.

The amino acid sequences of the 40 kD and 30-35 kD subunits recited in proposed count C is identical to those sequences recited in proposed counts A and B. There

is one difference between the subject matter of proposed counts A and C. Proposed count C contains the additional limitation "wherein said antibody is capable of blocking a biological activity of said protein," which is not found in proposed counts A and B.

B. Proposed Count B Is Directed To A Separately Patentable Invention From Proposed Count C

For the same reasons proposed count B is separately patentable over proposed count A, proposed count B is separately patentable over proposed count C. See Section III.B.

C. Proposed Count C Is Directed To A Separately Patentable Invention From Proposed Count A

As noted, the sole difference between proposed counts C and A is that proposed count C recites the additional limitation "wherein said antibody is capable of blocking a biological activity of said protein."

First, not all antibodies that react with IL-12 (*i.e.*, CLMF or NKSF) are capable of blocking a biological activity of IL-12. This is clearly demonstrated in Applicants' specification, which describes several antibodies that do not block a biological activity of IL-12. For example, at p. 75, ll. 19-28, the captioned application describes such non-blocking antibodies:

> Three inhibitory antibodies, 7B2, 2A3 and 4A1, and two non-inhibitory antibodies, 6A3 and 8E3, were purified from ascites fluid by protein G affinity chromatography on GammaBind G (Genex, Gaithersburg, MD) columns. Antibodies 4A1, 2A3 and 7B2 inhibit in a dose dependent manner ^{125}I-CLMF binding to the lymphoblasts with IC_{50} concentrations of 0.7 μg/ml, 7 μg/ml, and 9.5 μg/ml, respectively (Fig. 36). Antibodies 6A3 and 8E3 do not block ^{125}I-CLMF binding at concentrations of 100 μg/ml (Fig. 36). These data demonstrated that the original classification of each antibody as either inhibitory or non-inhibitory was correct.

Thus, the antibodies of proposed count C have properties that are new and unexpected as compared to the antibodies of proposed count A. Moreover, such antibodies capable of blocking (or neutralizing) the biological activity of IL-12 are useful in ways that non-blocking antibodies are not useful because non-blocking antibodies cannot eliminate the biological activity of IL-12 (Benjamin Dec., ¶ 13). It is the blocking antibodies that are clearly useful, for example, to lower the concentration of biologically active IL-12 so as to achieve the selective blockade of proliferation and activation of cytotoxic T cells, such as in transplantation (Benjamin Dec., ¶ 13). See the captioned application, p. 7, ll. 2-4. Non-blocking antibodies would not be expected to be useful for that therapeutic application in transplantation (Benjamin Dec., ¶ 13).

The new and different properties possessed by the antibodies of proposed count C, namely, they block a biological activity of IL-12 and have a therapeutic use that the antibodies of proposed count B would not be expected to have, renders that subject matter novel and nonobvious as compared to the subject matter of proposed count A. *In re Chupp*, 816 F.2d 643 2 USPQ2d 1437 (Fed. Cir. 1995); *In re Albrecht*, 514 F.2d 1389, 185 USPQ 585 (C.C.P.A. 1975).

Thus, the subject matter of proposed count C of Applicants' application Serial No. 10/267,565 is separately patentable from the subject matter of proposed count A in the captioned application.

V. TRINCHIERI IS NOT ENTITLED TO BENEFIT OF THE FILING DATE OF THE '945 APPLICATION FOR THE SUBJECT MATTER OF PROPOSED COUNT A OR B

The first-filed Trinchieri application identified on the front page of the '523 patent is application Serial No. 269,945, filed November 10, 1988 ("'945 application"). For the reasons given below, Trinchieri is not entitled to the benefit of the '945 application for the subject matter of proposed count A or B.

A. The '945 Application Does Not Disclose The Amino Acid Sequence Of Either IL-12 Subunit, So There Can Be No Written Description Of Proposed Counts A And B Which Recite Those Sequences

Proposed count A recites the amino acid sequences of both the 40 kD and 30-35 kD subunits of IL-12 and proposed count B recites the amino acid sequence of the 30-35 kD subunit. This reflects the *requirement* of the Examiner during prosecution of the '523 patent that the antibody claims recite the sequences of any subunit against which the antibody is directed. See the discussion of that requirement in Section II.A.1.

Thus, recitation of the complete amino acid sequence of each subunit recited in a claim was material to patentability of Trinchieri's claims because *without those limitations the claims would not have issued.* Similarly, the complete amino acid sequence of the subunits referenced in proposed counts A and B are material to the definition of the interfereing subject matter. A necessary corollary is that Trinchieri should not be entitled to benefit of a priority application unless that application discloses the complete amino acid sequence of each subunit recited in the count. *McBride v. Teeple*, 109 F.2d 789, 799, 44 USPQ 523, 533 (C.C.P.A. 1940) ("nothing is better settled in patent law than that in interference cases express limitations in counts may not be ignored."); *Meitzner v. Corte*, 537

F.2d 524, 530, 190 USPQ 407, 412 (C.C.P.A. 1976) (all limitations in interference counts "will be regarded as material to the invention covered by the counts.").

It is indisputable that the '945 application does not disclose the *complete* amino acid sequence of either the 40 kD subunit which is recited in proposed count A or the 30-35 kD subunit of IL-12, which is recited in proposed counts A and B. Therefore, the Trinchieri '945 application does not have a written description of the subject matter of the proposed counts. *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997) (finding no written description of a claim reciting "human insulin DNA" because "[n]o sequence information indicating which nucleotides constitute human cDNA appears in the patent.").

B. The '945 Application Teaches That IL-12 Is A Homodimer Of The 40 kD Subunit, So The Application Cannot Have A Written Description Of Proposed Count A, Which Describes IL-12 As A Heterodimer Of The 40 kD And 35 kD Subunits Or Proposed Count B Which Recites The 35 kD Subunit

The '945 application teaches that NKSF is a *homodimer* of the 40 kD subunit:

> These results indicate that the native NSF is a disulfide-bonded dimer (apparently a homodimer) of an approximately 40 kD species . . . .

'945 application, p. 26, ll. 5-7. Therefore, the '945 application does not even acknowledge that a 30-35 kD protein exists as a subunit of IL-12 (much less disclose the amino acid sequence of that subunit). Surely, that application cannot describe the subject matter of proposed count A, which recites a *heterodimeric* protein having both 40 kD and 30-35 kD subunits. And because the '945 application does not even acknowledge that a 35 kD subunit forms any part of the invention, it cannot have a written description of either proposed count A or B, both of which recite the 30-35 kD subunit.

C. The '945 Application Fails To Disclose Any Utility For Any Anti-IL-12 Antibodies And No Utility Is Obvious, So The Application Does Not Satisfy The Utility Requirement Or The "How To Use" Requirement For Proposed Counts A And B

In *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), the Supreme court found that an invention cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. The Court of Appeals for the Federal Circuit has outlined the proper analysis for inquiry into whether the "utility" requirement of 35 U.S.C. § 101 is met:

> a thorough analysis of the utility issue requires first, a determination as to what utility is disclosed, i.e., the stated utility, for the invention claimed in the application. Only after the stated utility has been determined, can a proper analysis be undertaken to determine if the stated utility complies with the 'practical utility' requirement of § 101.

Cross v. Iizuka, 753 F.2d 1040, 1044 n.8, 224 USPQ 739, 742 n.8 (Fed. Cir. 1985). Failure to meet the utility requirement of Section 101 also leads to a failure to teach how to use the invention under 35 U.S.C. § 112, first paragraph. *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (C.C.P.A. 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (C.C.P.A. 1971).

1. The '945 Application Fails To Describe A Utility For Antibodies That Specifically React With IL-12

There is only one statement in the '945 application describing uses for antibodies that specifically bind NKSF:

> Other uses for these novel polypeptides are in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

'945 application, p. 18, ll. 14-17 (emphasis added). This is the same single sentence that describes the antibodies themselves. While this sentence states that the antibodies can be used for "diagnostic or therapeutic use," it does not describe any *specific* use at all for one very simple reason: *the application fails to identify what disease or disorder can be diagnosed or therapeutically treated.*[10/] With no disease or disorder specified, the statement of "diagnostic or therapeutic use" is meaningless.

The mere statement in the '945 application that antibodies that specifically react with IL-12 are for "diagnostic or therapeutic" uses, with no disclosure of any disease or disorder that can be diagnosed or therapeutically treated, does not disclose a specific or substantial utility as required by 35 U.S.C. § 101. The case law firmly supports this conclusion.

For example, in *In re Kirk*, 376 F.2d 936, 153 USPQ 48 (C.C.P.A. 1967), the Court of Customs and Patent Appeals analyzed whether a general statement that the compounds of the count have "biological activity" satisfies the utility requirement. There the

---

10/ The only therapeutic uses that are described in the '945 application are exclusively limited to administration of NKSF *polypeptides*, subunits or fragments thereof ('945 application, p. 5, l. 18 to p. 6, l. 3, p. 18, l. 18 to p. 20, l. 14), not antibodies. The '945 application provides absolutely no teaching of a *specific* therapeutic use that involves an antibody which specifically reacts with NKSF.

application characterized the claimed compounds as "often possessing high biological activity" or that the compounds have value "on account of their biological properties or as intermediates in the preparation of compounds with useful biological properties," without identifying what kind of activity. *Kirk*, 376 F.2d at 938, 153 USPQ at 50. The court concluded:

> It seems to us that the nebulous expressions 'biological activity' or 'biological properties' appearing in the specification convey no more explicit indication of the usefulness of the compounds and how to use them than did the equally obscure expression "useful for 'technical and pharmaceutical purposes'" unsuccessfully relied upon by the appellant in In re Diedrich, 318 F.2d 946, 50 CCPA 1355 [138 USPQ 128 (C.C.P.A. 1963)].

Kirk, 376 F.2d at 941, 153 USPQ at 52.

In *Diedrich*, the application described the claimed compounds as "useful for 'technical and pharmaceutical purposes,' and that they possess certain *properties*, viz, high iodine content in a relatively stable bond, lack of color, and that their salts are non-toxic and relatively water-soluble." *In re Dietrich*, 318 F.2d 946, 949, 138 USPQ 128, 130 (C.C.P.A. 1963). The court concluded: "To say merely that an invention is useful as a pharmaceutical, even coupled with the recitation of certain properties, falls far short of satisfying the precise demands of section 112." *Diedrich*, 318 F.2d at 951, 138 USPQ at 131.

More recently, in *In re Brana*, 51 F.3d 1560, 1564-65, 34 USPQ2d 1436, 1440 (Fed. Cir. 1995), the Commissioner argued "that the disclosed uses in [Brana's] application, namely the 'treatment of diseases' and 'antitumor substances,' are similar to the nebulous disclosure found insufficient in *In re Kirk*" (citation omitted). While the court stated that "*Kirk* would be potentially dispositive of this case were the above-mentioned language the only assertion of utility," it noted another disclosure of utility that was found sufficient to meet Section 101. *Brana*, 51 F.3d at 1565, 34 USPQ2d at 1440.

Consistent with these cases, the Patent and Trademark Office ("PTO") has issued "Guidelines for Examination of Applications for Compliance With the Utility Requirement." *See* 66 Fed.Reg. 1092, 1097-99 (Jan. 5, 2001) ("PTO Guidelines"). The PTO Guidelines provide that an invention has utility if (1) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention and (2) the utility is *specific, substantial and credible*. 66 Fed.Reg. at 1098 (left column). The PTO has further issued "Revised Interim Utility Guidelines Training Materials" (available at http://www.uspto.gov/web/patents/guides.htm; "Training Materials")

for use by examiners in analyzing utility issues under the PTO Guidelines. Those Training Materials instruct:

> a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

Training Materials at 5-6. Additionally, the Training Materials list examples of situations that do not define "substantial utilities," including a method of treating an unspecified disease or condition. Training Materials at 6.

Thus, under the PTO Guidelines and Training Materials, the failure of the '945 application to specify any disease or disorder that may be diagnosed or therapeutically treated mandates that the application does not provide a specific or substantial utility as required by Section 101.

Kirk, *Diedrich*, *Brana* and the PTO Guidelines and Training Materials are directly applicable to the facts here. Trinchieri's statement that the antibodies may be used for "diagnostic or therapeutic uses" provides insufficient indication regarding utility because one skilled in the art would not know what disease or disorder could be diagnosed or therapeutically treated with antibodies to NKSF. The application does not even address or speculate whether any disease or disorder is *caused* by or at least involves an abnormal level of NKSF and, therefore, might possibly be amenable to diagnosis via NKSF measurement or to treatment via anti-NKSF antibody administration.

Importantly, the '945 application fails to provide any teaching regarding what levels of NKSF are produced either normally or in any disease or disorder, which is information that would be necessary for one of skill in the art to utilize NKSF antibodies to diagnose or treat any specific disease or disorder. Further, this information was not within the state of the art at the time the '945 application was filed. This is acknowledged by the November 1992 publication by D'Andrea *et al.*, 1992, J. Exp. Med. 176: 1387-1398 ("D'Andrea *et al.*;" Exhibit I), co-authored by a subset of the inventors of the '523 patent, which states that prior to the study reported in the publication, nothing had been known about the production of NKSF (IL-12) in normal blood cells (D'Andrea *et al.*, p. 1388, left column).

Further, the '945 application fails to teach that an NKSF antibody-based diagnostic use would be operable only when certain types or sets of NKSF antibodies exhibiting particular characteristics are employed. This is because conditions that promote production of biologically active NKSF heterodimer also promote production and secretion of free NKSF 40 kD subunit, which does not exhibit the heterodimeric activity. Thus, any

useful diagnostic assay would have to distinguish between the heterodimeric NKSF and the free NKSF 40 kD subunit (Second Presky Dec., ¶ 11).

Specifically, conditions that stimulate production of biologically active NKSF heterodimer also induce production of a large excess free 40 kD NKSF subunit (Benjamin Dec., ¶ 16). See, *e.g.*, Chizzonite *et al.*, 1991, J. Immunol. 147: 1548-1556 ("Chizzonite *et al.*;" Exhibit J), p. 1555, paragraph bridging left and right columns; and D'Andrea *et al.* (Exhibit I), Figs. 4A-4B, p. 1392, and accompanying text. The 40 kD subunit alone, however, exhibits no biological activity (Benjamin Dec., ¶ 16). See, *e.g.*, Chizzonite *et al.*, Table III, p. 1553; and D'Andrea *et al.*, Figs. 4A-4B, p. 1392, and accompanying text. Thus, a successful antibody-based diagnostic use would require employing an antibody that can distinguish between the 70 kD NKSF heterodimer and the free 40 kD NKSF subunit (Benjamin Dec., ¶ 16).

The '945 application, however, is silent on these points and provides absolutely no written description regarding particular sorts of antibodies (*e.g.*, an antibody which reacts specifically with the 70 kD heterodimer, but not either of the subunits or, alternatively, a combination of antibodies that, together, can distinguish between the 70 kD heterodimer) that could be successful in an NKSF diagnostic context.

In the complete absence of teaching relating to normal NKSF levels or any indication that any particular disease state or disorder is or even may be caused by abnormal levels of NKSF, the '945 application fails to even suggest *any* diagnostic or therapeutic use, let alone a *specific* diagnostic or therapeutic use for an antibody which specifically binds NKSF. As pointed out in D'Andrea *et al.*, it was only by producing antibodies which specifically bind NKSF that an investigation was carried out to determine the levels of production or NKSF by normal blood cells. Essentially, then, Trinchieri acknowledges in D'Andrea *et al.* that, for a practical diagnostic or therapeutic use for NKSF antibodies, it would have been necessary for one of skill in the art to first make antibodies and then do extensive characterization and experimentation before amassing the basic information that would have been necessary to embark on development of a diagnostic or therapeutic use for such antibodies. This, however, is not sufficient for fulfilling the utility requirement. A "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).

Thus, under applicable legal precedent and the PTO's own Guidelines and Training Materials, the '945 application does not disclose a practical utility for the antibodies

of the count, as required by Section 101, and does not teach how to use those antibodies, as required by Section 112, first paragraph.

2. There Is No Obvious Utility For Antibodies That Specifically React With IL-12

To the extent antibodies that specifically react with IL-12 could be made based upon the disclosure of the '945 application, there would have been no obvious utility for them. Specifically, antibodies that might have been made using the information in the '945 application would *not* have had utility in purifying IL-12 because they would not distinguish between IL-12 heterodimer and the free 40 kD subunit that is present in excess in biological samples. Therefore, they could not be used to selectively purify IL-12 heterodimer from the subunit to increase the proportion of IL-12, *i.e.*, they could not be used to obtain purified IL-12.

More specifically, the '945 application discloses a method that purports to partially purify IL-12 (see, for example, '945 application, p. 21, l. 12, to p. 24, l. 20). See Benjamin Dec., ¶ 17. Note, however, that the free 40 kD subunit is present in excess in biological samples, and is also present in the partially purified IL-12 preparation described in the '945 application (Benjamin Dec., ¶ 17). Any such partially purified IL-12 preparation containing excess free 40 kD subunit, if used to elicit antibodies, would result in antibody preparations against both the free 40 kD subunit and IL-12 (Benjamin Dec., ¶ 17). Such antibody preparations would co-purify the free 40 kD subunit and IL-12 and could not be used to selectively purify IL-12 (Benjamin Dec., ¶ 17). Moreover, such resulting mixed preparations of IL-12 and free 40 kD subunit would not provide a suitable material for therapeutic applications (Benjamin Dec., ¶ 17).

This conclusion is corroborated by the results reported in D'Andrea *et al.* (Exhibit I) and in Chizzonite *et al.* (Exhibit J), both of which were discussed in Section III.B. Both D'Andrea *et al.* and Chizzonite *et al.* concern generation of antibodies directed against IL-12 (*i.e.*, NKSF or CLMF) and both of these publications report that when a purified sample of IL-12 heterodimer is used as the starting antigen one obtains antibodies that react with both the heterodimer and the free 40 kD subunit. Specifically, D'Andrea *et al.* show that antibodies generated against recombinantly produced NKSF heterodimer (referred to in D'Andrea *et al.* as "C11" antibodies) exhibit a reactivity pattern similar to antibodies generated against just the NKSF 40 kD subunit (referred to in D'Andrea *et al.* as the "C8

series" of antibodies), *i.e.*, they react with the 40 kD subunit (D'Andrea *et al.*, p. 1390, left column, and Fig. 1), which means they also react with IL-12 because it contains that subunit.

Chizzonite *et al.* reports on monoclonal and polyclonal antibodies directed against IL-12 (NKSF or CLMF) generated using purified or partially purified NKSF heterodimer (Benjamin Dec., ¶ 14). The results presented in Chizzonite *et al.* demonstrate that using purified NKSF resulted only in the generating of antibodies which specifically bind the 40 kD subunit (Chizzonite *et al.*, p. 1554, left column). See Benjamin Dec., ¶ 14. That is, no antibodies were produced which specifically react with the 30-35 kD subunit (Benjamin Dec., ¶ 14). In attempting to explain the reason for the apparent preference for antibodies directed against the 40 kD subunit, Chizzonite *et al.* points out that significant amounts of the free 40 kD subunit are present in purified IL-12 samples, which can bias toward identification of antibodies against the 40 kD subunit (Chizzonite *et al.*, p. 1555, left column). See Benjamin Dec., ¶ 14.

The '945 application also discloses six peptides, each ranging in size from five to eight amino acid residues in length (see '945 application, p. 3, ll. 16-20; p. 11, ll. 12-17; and p. 27, ll. 5-10; the six sequences on each page are identical), then thought to be part of the amino acid sequence of IL-12 (Benjamin Dec., ¶ 18). Three of those peptides are now known (but were not then known) to be found within the 30-35 kD subunit (Benjamin Dec., ¶ 18). See the three sequences at p. 11, ll. 14, 16 and 17 of the '945 application. Today it is clear from the amino acid sequences of Figs. 2A-2C of the '523 patent (col. 6, ll. 13-17) that these sequences correspond to the underlined amino acid residues 180-184, 246-252 and 81-88, respectively (Benjamin Dec., ¶ 18). In addition, it is now known (but was not then known) that the remaining sequences at p. 11, ll. 12, 13 and 15 of the '945 application are found within the 40 kD subunit (Benjamin Dec., ¶ 18). See the '523 patent, Figs. 1A-1D, which shows that these sequences correspond to amino acids 75-79, 219-224 (with a mistake at 222) and 23-27 of the 40 kD subunit (Benjamin Dec., ¶ 18).

It would have been difficult and uncertain as to whether one could elicit antibodies to a protein containing any of such peptides, even if the peptide were to be conjugated to a carrier protein (Benjamin Dec., ¶ 19). The quality and specificity of such antibodies would also be doubtful (Benjamin Dec., ¶ 19). Rather, a peptide of five to eight amino acids, generally, a peptide of at least approximately ten amino acids, would be used in generating antibodies (Benjamin Dec., ¶ 19). Thus, it would have been difficult and uncertain

as to whether one could elicit antibodies specific for IL-12 using those peptides of the 30-35 kD subunit disclosed in the '945 application (Benjamin Dec., ¶ 19).

Therefore, none of the antibodies enabled in the '945 application would have been able to selectively purify IL-12 heterodimer from free 40 kD subunit.

D. The '945 Application Fails To Describe How To Make Antibodies To The 30-35 kD Subunit, So There Can Be No Written Description Or Enablement For Proposed Count B

The '945 application contemplates using "standard methods" to make monoclonal and polyclonal antibodies to NKSF with absolutely no discussion of what those methods may be:

> Other uses for these novel polypeptides are in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

'945 application, p. 18, ll. 14-17 (emphasis added). That sentence is the *sole disclosure* relating to antibodies.

Standard methods for making polyclonal antibodies would involve administration of the protein of interest to an animal from which one would expect to obtain serum that would react with the protein. For monoclonal antibodies, standard methods would next involve isolation of antibody producing cells from that animal and fusing them with myeloma cells to make hybridomas, as was done in Applicants' Example 13 (captioned application, p. 71, l. 7 to 72, ll. 6). Clearly, one would have to first make polyclonal antibodies to IL-12 before monoclonal antibodies could be made.

However, Applicants' use of that "standard method" did not result in the production of polyclonal antibodies within the scope of proposed count B. The data in Applicants' specification (p. 73, l. 20 to p. 74, l. 9) demonstrates that all of the 20 monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9). Since the technique for making those monoclonals involves random selection from all antibodies in the polyclonal serum, any such polyclonal preparation would have antibodies that react with the 40 kD subunit. Thus, one would not obtain a polyclonal antibodies that *specifically react* with the 30-35 kD subunit. And without such polyclonal antibodies, one would not expect to isolate antibody-

producing cells to fuse to myeloma cells to make hybridomas for the production of monoclonal antibodies that specifically react with the 30-35 kD subunit.

Note: The following seven paragraphs are repeated from Section III.B since they are equally pertinent here.

The data in Applicants' specification (p. 73, l. 20 to p. 74, l. 9) demonstrates that all of the 20 monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9). Since none of those antibodies specifically bound to the 30-35 kD subunit, antibodies to the 30-35 kD subunit would not have been obvious, even assuming antibodies to the 75 kD heterodimer and the 40 kD subunit were in the prior art.

The data of Applicants' specification is consistent with the conclusions of Applicants' expert, David H Presky, Ph.D.[11/] See the Second Declaration of Dr. David H. Presky, filed July 24, 2000 ("Second Presky Declaration;" attached as Exhibit H). Making antibodies, especially monoclonal antibodies, which specifically bind the NKSF 30-35 kD subunit is difficult, and clearly not routine, when using purified NKSF or reconstituted NKSF heterodimer as the antigen (Second Presky Dec., ¶ 7). This fact is illustrated by the results reported in D'Andrea *et al.*[12/] and in Chizzonite *et al.*,[13/] a scientific paper co-authored in 1991 by a subset of the Applicants of the captioned application.

Both D'Andrea *et al.* and Chizzonite *et al.* concern generation of antibodies directed against IL-12 (*i.e.*, NKSF or CLMF) and both of these publications point out the difficulties associated with attempting to produce antibodies which specifically bind to the NKSF 30-35 kD subunit when a purified sample of NKSF heterodimer is used as the starting antigen. The results in D'Andrea *et al.* show that antibodies generated against recombinantly produced NKSF heterodimer (referred to in D'Andrea *et al.* as "C11" antibodies) fail to react

---

11/ Dr. Presky's qualifications as an expert are found in his declaration, ¶¶ 1-5.

12/ D'Andrea *et al.*, 1992, "Production of Natural Killer Cell Stimulatory Factor (Interleukin 12) by Peripheral Blood Mononuclear Cells," J. Exp. Med. 176: 1387-1398 (attached as Exhibit I).

13/ Chizzonite *et al.*, 1991, "IL-12: Monoclonal Antibodies Specific for the 40 kDa Subunit Block Receptor Binding and Biologic Activity of Activated Human Lymphoblasts," J. Immunol. 147: 1548-1556 (attached as Exhibit J).

with the 30-35 kD NKSF subunit and exhibit a reactivity pattern similar to antibodies generated against just the NKSF 40 kD subunit (referred to in D'Andrea *et al.* as the "C8 series" of antibodies), *i.e.*, only react with the 40 kD subunit (D'Andrea *et al.*, p. 1390, left column, and Fig. 1).

Chizzonite *et al.* reports on monoclonal and polyclonal antibodies directed against IL-12 (NKSF or CLMF) generated using purified or partially purified NKSF heterodimer (Benjamin Dec., ¶ 14). The results presented in Chizzonite *et al.* demonstrate that using purified NKSF resulted only in the generating of antibodies which specifically bind the 40 kD subunit (Chizzonite *et al.*, p. 1554, left column). See Benjamin Dec., ¶ 14. That is, no antibodies were produced which specifically react with the 30-35 kD subunit (Benjamin Dec., ¶ 14). In attempting to explain the reason for the apparent preference for antibodies directed against the 40 kD subunit, Chizzonite *et al.* points out that significant amounts of the free 40 kD subunit are present in purified IL-12 samples, which can bias toward identification of antibodies against the 40 kD subunit (Chizzonite *et al.*, p. 1555, left column). See Benjamin Dec., ¶ 14. Chizzonite *et al.* also reports that, apparently, antibodies against the 30-35 kD subunit arise "only after multiple immunizations," as opposed to antibodies against the 40 kD subunit, which arise very rapidly (Chizzonite *et al.*, p. 1555, left column). See Benjamin Dec., ¶ 14.

The techniques required by Chizzonite *et al.* to generate antibodies against the 30-35 kD subunit are not standard techniques that would have been utilized by one of skill in the art (Benjamin Dec., ¶ 15). Rather, using standard techniques, one skilled in the art, upon observing that immunized animals produced a sufficient titer of polyclonal antibodies that specifically react with IL-12, would have terminated the immunization schedule and sacrificed the animal (Benjamin Dec., ¶ 15). Thus, using standard techniques, further multiple immunizations would not have been done and antibodies specific for the 30-35 kD subunit would not have been made (Benjamin Dec., ¶ 15).

Clearly, then, the results presented in both D'Andrea *et al.* and Chizzonite *et al.* demonstrate that when "standard" methods, such as using purified NKSF antigen, are employed to produce antibodies that recognize the 40 kD subunit as well as antibodies that recognize the 30-35 kD subunit, such methods fail to yield antibodies that specifically react with the 30-35 kD subunit.

Moreover, in order to make antibodies that specifically bind to the 30-35 kD subunit, Applicant first cloned the DNA encoding that subunit and from the DNA sequence

of that clone selected an 11-amino acid sequence within the encoded mature protein to use as an immunogen to raise antibodies (p. 79, ll. 6-8). That 11-amino acid sequence was chemically synthesized and conjugated to keyhole limpet hemocyanin and the conjugate was used to immunize rabbits (p. 79, ll. 8-15). Serum from the rabbits contained antibodies that specifically react with the 30-35 kD subunit and also reacted with IL-12 (p. 79, ll. 1-10). However, sufficient amino acid sequence information for the 30-35 kD subunit of IL-12 was not available in the art in 1990.

The '945 application also discloses six peptides, each ranging in size from five to eight amino acid residues in length (see '945 application, p. 3, ll. 16-20; p. 11, ll. 12-17; and p. 27, ll. 5-10; the six sequences on each page are identical), then thought to be part of the amino acid sequence of IL-12 (Benjamin Dec., ¶ 18). Three of those peptides are now known (but were not then known) to be found within the 30-35 kD subunit (Benjamin Dec., ¶ 18). See the three sequences at p. 11, ll. 14, 16 and 17 of the '945 application. Today it is clear from the amino acid sequences of Figs. 2A-2C of the '523 patent (col. 6, ll. 13-17) that these sequences correspond to the underlined amino acid residues 180-184, 246-252 and 81-88, respectively (Benjamin Dec., ¶ 18). In addition, it is now known (but was not then known) that the remaining sequences at p. 11, ll. 12, 13 and 15 of the '945 application are found within the 40 kD subunit (Benjamin Dec., ¶ 18). See the '523 patent, Figs. 1A-1D, which shows that these sequences correspond to amino acids 75-79, 219-224 (with a mistake at 222) and 23-27 of the 40 kD subunit (Benjamin Dec., ¶ 18). It would have been difficult and uncertain as to whether one could elicit antibodies to a protein containing any of such peptides, even if the peptide were to be conjugated to a carrier protein (Benjamin Dec., ¶ 19). The quality and specificity of such antibodies would also be doubtful (Benjamin Dec., ¶ 19). Rather, a peptide of five to eight amino acids, generally, a peptide of at least approximately ten amino acids, would be used in generating antibodies (Benjamin Dec., ¶ 19). Thus, it would have been difficult and uncertain as to whether one could elicit antibodies specific for IL-12 using those peptides of the 30-35 kD subunit disclosed in the '945 application (Benjamin Dec., ¶ 19).

See also, *e.g.*, Harlow & Lane, a 1988 laboratory manual of techniques for antibody production and use that reflects the state of the art in 1988. *Antibodies: A Laboratory Manual*, 1988, (Harlow, E. & Lane, D., eds.) Cold Spring Harbor Laboratory, New York; p. 76 ("Harlow & Lane;" attached as Exhibit M). As pointed out in Harlow & Lane, while synthetic peptides as short as six amino acids can be used to produce antibodies

to a protein containing that sequence, the antibody response with such short sequences vary and standard methods teach that peptides of at least approximately ten amino acids should be used.

Finally, one skilled in the art would not have even attempted to use any material isolated from a reducing SDS gel having a molecular weight of approximately 30-35 kD to produce an antibody to NKSF *because the '945 application teaches that NKSF is a homodimer of the 40 kD subunit only*. Therefore, there is no suggestion in the '945 application to even attempt to make antibodies to the 30-35 kD subunit.

Given the meager disclosure of the '945 application, standard methods could not be used to obtain any antibodies within the scope of proposed count B. Therefore, the Trinchieri '945 application does not provide a written description of how make antibodies that specifically react with the 30-35 kD subunit. For the same reasons, the '945 application does not provide an enabling disclosure of any antibodies within the scope of proposed count B. Trinchieri is not entitled to the benefit of the '945 application for the subject matter of the proposed count B.

VI. TRINCHIERI IS NOT ENTITLED TO BENEFIT OF THE FILING DATE OF THE '817 APPLICATION FOR THE SUBJECT MATTER OF PROPOSED COUNTS A AND B

The second-filed Trinchieri application identified on the front page of the '523 patent is application Serial No. 307,817, filed February 7, 1989 ("'817 application"). For the reasons given below, Trinchieri is not entitled to the benefit of the '817 application for the subject matter of proposed counts A or B.

A. The '817 Application Does Not Disclose The Amino Acid Sequence Of Either IL-12 Subunit, So There Can Be No Written Description Of Proposed Counts A Or B Which Recite Those Sequences

As noted in Section II.A.1, proposed counts A and B properly list the complete amino acid sequences of the recited subunits. However, the '817 application does not disclose the complete amino acid sequence for either subunit.

The largest amino acid sequence (deduced from the largest nucleotide sequence) in the '817 application for the NKSF protein is for the 40 kD subunit. '817 application, p. 15, ll. 16-18. That amino acid sequence totals only 291 amino acids, including the 22 amino acid signal sequence, which is less than all of the total of 328 amino acids of the

40 kD subunit (including the signal sequence). See subpart (a) of proposed count A which recites a total of 306 amino acids not including the 22 amino acids of the signal sequence.

With respect to the 30-35 kD sequence, the '817 application discloses the same three amino acid sequences disclosed in the '945 application and states that they are part of the 30-35 kD subunit. See p. 5, l. 9; p. 35, ll. 1-2. Clearly, that does not constitute disclosure of the complete 197-amino acid sequence of the 30-35 kD subunit recited in proposed counts A and B.

Indisputably, the '817 application does not disclose the complete amino acid sequence for either subunit. Based on *McBride*, *Meitzner* and *Eli Lilly*, the Trinchieri '817 application does not provide a written description of the subject matter of either proposed count A or proposed count B because it does not disclose the complete amino acid sequences recited in those proposed counts.

B. The '817 Application Equivocates Among The Possibilities That IL-12 Is A Heterodimer Of The 40 kD And 35 kD Subunits Or A Homodimer Of Either Subunit, So The Application Cannot Have A Written Description Of Proposed Count A, Which Describes IL-12 As A Heterodimer Of Those Subunits, Or Proposed Count B, Which Recites The 35 kD Subunit

The '817 application does not specify whether NKSF is a heterodimer of the 40 kD and 35 kD subunits, a homodimer of the 40 kD subunit or a homodimer of the 35 kD subunit:

> Pure preparations of NKSF reveal the presence of two polypeptides, which are contemplated as subunits which, when associated, yield active NKSF. It is presently speculated that NKSF is a heterodimer formed by association of both the larger and smaller subunits through one or more disulfide bonds. . . . Alternatively, it is possible that the active form of NKSF is a homodimer of the larger subunit or a homodimer of the smaller unit.

'817 application, p. 3, l. 17 to p. 4, l. 3 (emphasis added).

Because the '817 application equivocates among the three possibilities for the dimeric structure of IL-12, it cannot be said to disclose any one of them in the manner required for a written description of proposed counts A and B, which identify IL-12 as a *heterodimer* having 40 kD and 30-35 kD subunits.

C. The '817 Application Fails To Disclose Any Utility For Any Anti-IL-12 Antibodies And No Utility Is Obvious, So The Application Does Not Satisfy The Utility Requirement Or The "How To Use" Requirement For Proposed Counts A And B

1. The '817 Application Fails To Describe A Utility For Antibodies That Specifically React With IL-12

The only use disclosed in the '817 application is identical to that in the '945 application:

> Other uses for these novel polypeptides are in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

'817 application, p. 25, ll. 8-11 (emphasis added). As for the '945 application, there is no description of any specific diagnostic use for antibodies that react with NKSF, and the only therapeutic uses that are described in the application are exclusively limited to administration of NKSF *polypeptides*, subunits or fragments thereof ('817 application, p. 7, l. 18 to p. 8, l. 4, p. 25, ll. 1-3, p. 25, l. 12 to p. 27, l. 12), not antibodies. The '817 application provides absolutely no teaching of a *specific* diagnostic or therapeutic use that involves an antibody which specifically reacts with NKSF.

Therefore, the entirety of argument and analysis found in Section V.C.1 applies to the '817 application. Consequently, the '817 application does not disclose a practical utility for the antibodies of proposed counts A and B, as required by Section 101, and does not teach how to use those antibodies, as required by Section 112, first paragraph.

2. There Is No Obvious Utility For Antibodies That Specifically React With IL-12

As noted in Section V.C.2, the antibodies that might have been made using the information in the '945 application would not have been useful to prepare more highly purified IL-12. Since the antibodies that might have been made using the information in the '817 application are, at best, the same as those in the '945 application, the result would have been the same. This is supported in the immediately following section which demonstrates that, at best, only antibodies that specifically react with the 40 kD subunit could be made based on the '817 application. Consequently, the analysis of Section V.C.2 applies to the '817 application as well. There is no obvious utility for any antibodies that might have been made from the disclosure of the '817 application.

Because the '817 application does not satisfy the utility or "how to use" requirement of 35 U.S.C. § 112 for the subject matter of proposed counts A and B, Trinchieri

is not entitled to rely on that application as a constructive reduction to practice of proposed count A or proposed count B.

D. The '817 Application Fails To Describe How To Make Antibodies To The 30-35 kD Subunit, So There Can Be No Written Description Or Enablement For Proposed Count B

The written description for polyclonal and monoclonal antibodies that specifically react with NKSF is the same in the '945 and '817 applications. It merely suggests to use standard methods. '817 application, p. 25, ll. 8-11; '945 application (p. 18, ll. 14-17). Several new peptide sequences from within NKSF were added in the '817 application, p. 4, ll. 17-19 and 25, p. 5. l. 9, also found at p. 35, ll. 1-2 and Table I at pp. 16-17). Of these new sequences, only the allegedly amino terminal sequence at p. 5, l. 9 is now known to be within the 30-35 kD subunit. See '523 patent, col. 6, ll. 13-14, which states that only sequence 4, 5 and 6 are within the 30 kD subunit. Below is a comparison of that new amino acid sequence (top row) with sequences now known to be present in the 30-35 kD subunit (bottom row), with the position in the mature sequence indicated above the amino acid:

2	3	4	5	6	7	8	9	10	11	12	13	14
Asn	Leu	Pro	Val	Ala	**Pro**	Pro	Asp	Pro	**[Ser or Thr]**	Met	Phe	Pro
Asn	Leu	Pro	Val	Ala	**Thr**	Pro	Asp	Pro	**Gly**	Met	Phe	Pro

See Benjamin Dec., ¶ 20.

It is readily apparent that there were two mistakes in this amino acid sequence of the '817 application, at positions 7 and 11 (Benjamin Dec., ¶ 21). The longest correct sequence within it is five residues, which is unlikely to elicit antibodies that specifically react with the 30-35 kD subunit, even if it were conjugated to a carrier protein (Benjamin Dec., ¶ 21).

Moreover, one skilled in the art would have considered it even less likely to elicit antibodies that specifically react with the 30-35 kD subunit using the entire 13-amino acid peptide of the '817 application, even if it were conjugated to a carrier protein because the incorrect sequence of the 13-amino acid peptide significantly increases the possibility that antibodies raised against a peptide having that sequence would cross-react with other proteins (Benjamin Dec., ¶ 21). Specifically, if antibodies were raised against the 13-amino acid peptide that also bound to the correct sequence of the 30-35 kD subunit, this would confirm that they lacked specificity for the 30-35 kD subunit (Benjamin Dec., ¶ 21). Thus, at best, the antibody preparations that could be made using the disclosure provided in the '817

application would be ones that react with the free 40 kD subunit and with the 40 kD subunit present in IL-12 (Benjamin Dec., ¶ 21).

Therefore, since standard methods would not permit one skilled in the art to make antibodies that specifically react with IL-12, and no further written description is presented in the '817 application teaching how to make such antibodies, Trinchieri is not entitled to the benefit of the '817 application for the subject matter of proposed count B. For the same reasons, the '817 application does not provide an enabling disclosure of any antibodies withing the scope of proposed count B.

VII. APPLICANTS ARE ENTITLED TO THE BENEFIT OF THE AUGUST 27, 1990 FILING DATE OF THEIR '284 APPLICATION FOR PROPOSED COUNTS A AND B

As noted above, the captioned application is a divisional application of the '151 application, which is a divisional application of the '011 application, which is a divisional of the '023 application, which is a continuation-in-part of the '284 application, filed August 27, 1990. Because application Serial No. 07/572,284 meets the written description and enablement requirements of 35 U.S.C. § 112, first paragraph, for at least one species within proposed count A and at least one species within proposed count B, Applicants are entitled to the benefit of the August 27, 1990 filing date for both counts. *Squires v. Corbett*, 560 F.2d 424, 433, 194 USPQ 513, 519 (C.C.P.A. 1977); *Weil v. Fritz*, 572 F.2d 856, 865-66 n.16, 196 USPQ 600, 608 n.16 (C.C.P.A. 1978).

A. Applicants' '284 Application Describes A Constructive Reduction To Practice Of Many Species Within Proposed Count A

The '284 application discloses that CLMF is a heterodimer made up of a first subunit having the amino acid sequence recited in part (a) of proposed count A and an apparent molecular weight of approximately 40 kD and a second subunit having the amino acid sequence recited in part (b) of proposed count A and an apparent molecular weight of approximately 35 kD, both molecular weights measured under reducing conditions on SDS PAGE. '284 application, p. 33, ll. 11-18. See also '284 application, p. 4, ll. 27-30 and original claims 10-12.

The amino acid sequence recited in part (a) of proposed count A for the 40 kD subunit is found in Fig. 25 of the '284 application, beginning at amino acid 23 and continuing to amino acid 328. '284 application, p. 66, ll. 22-30. The amino acid sequence recited in part (b) of proposed count A and proposed count B for the 30-35 kD subunit, wherein X is Gly,

Y is Thr and Z is Thr, is found in Fig. 26 of the '284 application, beginning at amino acid 23 and continuing to amino acid 219. '284 application, p. 69, l. 28 to p. 70, l. 5.

The '284 application provides an enabling disclosure for antibodies that specifically react with such heterodimeric CLMF. Example 13 (pp. 74-82; summarized at pp. 5-6) describes the successful generation and characterization of monoclonal antibodies directed against CLMF. The rats were immunized with partially purified CLMF (p. 74, ll. 3-6). At p. 75, ll. 15-24, the specification states:

> Four individual monoclonal antibodies also immunoprecipitated the 75 kDa heterodimer and the free 40 kDa subunit (Fig. 28) but did not immunoprecipitate the 92 kDa or 25 kDa labelled proteins [which were contaminants in the CLMF preparation]. The immunoprecipitation assay identified twenty hybridomas which secreted anti-CLMF antibodies (Table 15). All the antibodies immunoprecipitated the radiolabeled 75 kDa heterodimer and the free 40 kDa subunit as determined by SDS/PAGE and autoradiography (data shown for 4 representative antibodies in Fig. 28).

Because the specification describes and enables the monoclonal antibody claims (as described immediately above), and corresponding polyclonal antibodies are made as an early part of preparing the monoclonal antibodies, such polyclonal antibodies are also supported in the captioned application. See, for example, '284 application, p. 74, l.31 to p. 75, l. 3.

The '284 application also describes the production of monoclonal antibodies which specifically react with either the 40 kD subunit or the 30-35 kD subunit (p. 5, l. 10 to p. 6, l. 6; Example 13, pp. 74-82; Example 14, pp. 83-85) and ample methods for assaying such anti-CLMF antibodies (p. 28, l. 6 to p. 31, l. 30).

With respect to the practical utility of such CLMF antibodies, the '284 application describes several practical utilities (p. 6, l. 8 to p. 7, l. 15). In particular, Applicants point to the following specific utility:

> 5. Utilizing the intact IgG molecules, the Fab fragments or the humanized IgG molecules of the inhibitory monoclonal antibodies as <u>therapeutic drugs for the selective blockade of proliferation and activation of cytotoxic T cells, such as in transplantation</u>.

'284 application, p. 7, ll. 8-12 (emphasis added).

Thus, unlike the specifications of the Trinchieri '817 and '945 applications, the specification of the '284 application teaches one of skill in the art a *specific* utility for the anti-CLMF antibodies of proposed count A, namely, use of the anti-CLMF monoclonal antibodies for the selective *blockade* of the proliferation and activation of cytotoxic T cells,

such as would be beneficial when utilized as part of transplantation procedures ('284 application, p. 7, ll. 8-12).

Therefore, Applicants' '284 application provides a constructive reduction to practice of at least one species within proposed count A. As such, Applicants are entitled to the benefit of the August 27, 1990 filing date of the '284 application for proposed count A.

B. Applicants' '284 Application Describes A Constructive Reduction To Practice Of Many Species Within Proposed Count B

The '284 application discloses that CLMF is a heterodimer made up of a first subunit having the amino acid sequence recited in part (a) of proposed count A and an apparent molecular weight of approximately 40 kD and a second subunit having the amino acid sequence recited in part (b) of proposed count A and an apparent molecular weight of approximately 35 kD, both molecular weights measured under reducing conditions on SDS PAGE. '284 application, p. 33, ll. 11-18. See also '284 application, p. 4, ll. 27-30 and original claims 10-12.

The amino acid sequence recited in proposed count B for the 30-35 kD subunit, wherein X is Gly, Y is Thr and Z is Thr, is found in Fig. 26 of the '284 application, beginning at amino acid 23 and continuing to amino acid 219. '284 application, p. 69, l. 28 to p. 70, l. 5.

Example 14 of the '284 application (pp. 83-85) describes a method for producing monoclonal antibodies which specifically react with the 35 kD CLMF subunit, wherein the monoclonal antibodies are generated against a synthetic peptide containing a 35 kD CLMF subunit amino acid sequence.

With respect to the practical utility of such CLMF antibodies, the '284 application describes several practical utilities (p. 6, l. 8 to p. 7, l. 15). In particular, Applicants point to the following specific utility:

> 5. Utilizing the intact IgG molecules, the Fab fragments or the humanized IgG molecules of the inhibitory monoclonal antibodies as <u>therapeutic drugs for the selective blockade of proliferation and activation of cytotoxic T cells, such as in transplantation</u>.

'284 application, p. 7, ll. 8-12 (emphasis added).

Thus, unlike the specifications of the Trinchieri '817 and '945 applications, the specification of the '284 application teaches one of skill in the art a *specific* uitility for the anti-CLMF antibodies of proposed count B, namely, use of the anti-CLMF monoclonal antibodies for the selective *blockade* of the proliferation and activation of cytotoxic T cells,

such as would be beneficial when utilized as part of transplantation procedures ('284 application, p. 7, ll. 8-12).

Thus, the '284 application provides a constructive reduction to practice of at least one species within proposed count B. As such, Applicants are entitled to the benefit of the August 27, 1990 filing date of the '284 application for proposed count B.

VIII. THE REQUESTED INTERFERENCE SHOULD BE DECLARED BECAUSE APPLICANTS' EFFECTIVE FILING DATE IS PRIOR TO THE EFFECTIVE FILING DATE OF THE '523 PATENT FOR PROPOSED COUNTS A AND B

Applicants have established above that their effective filing date for the subject matter of proposed counts A and B is August 27, 1990 and the earliest possible effective filing date of the '523 patent for proposed counts A and B is September 18, 1990. Since Applicants' effective date is prior to the earliest possible effective filing date of the '523 patent for the subject matter of proposed counts A and B, no statement under 37 C.F.R. § 1.608 should be necessary. *See* 37 C.F.R. §§ 1.608(a) and (b) (requiring showings under either section *only* if the application is filed *after* the effective filing date of the patent). Nevertheless, in the event a showing under 37 C.F.R. § 1.608(a) is required, an appropriate Declaration of Thomas E. Friebel accompanies this Request.

IX. APPLICANTS' CLAIM TO *PRIMA FACIE* ENTITLEMENT TO JUDGMENT IN A RULE 608(b) REQUEST MAY BE BASED ON UNPATENTABILIITY OF THE INTERFERING SUBJECT MATTER TO THE PATENTEE

In a Rule 608(b) request, unpatentability to the patentee of the subject matter proposed for the interference may be raised as a basis for an applicant's prima facie entitlement to judgment. Specifically, where an applicant seeks declaration of an interference, and the effective filing date of an application is more than three months after the effective filing date of a patent, Rule 608(b) requires the applicant to:

> file evidence which may consist of patents or printed publications, other documents, and one or more affidavits which demonstrate that applicant is prima facie entitled to a judgment relative to the patentee and an explanation stating with particularity the basis upon which the applicant is prima facie entitled to the judgment.

37 C.F.R. § 1.608(b). The administrative history of Rule 608(b) clearly indicates that the basis for an applicant's entitlement to the judgment may be unpatentability of the interfering subject matter to the patentee, and need not be priority of invention:

> Under § 1.608, the PTO will continue current practice (37 CFR 1.204(c)) of requiring an applicant seeking to provoke an interference with a patent to submit evidence which demonstrates that the applicant is prima facie entitled to a judgment relative to the patentee. Evidence would be submitted only when the earlier of the filing date or effective filing date of the application is more than three months after the earlier of the filing date or effective filing date under 35 U.S.C. 120 of the patent. The evidence may relate to patentability and need not be restricted to priority.

49 Fed. Reg. 48416, 48421 (Dec. 12, 1984) (emphasis added). This has been recently confirmed by the Board in *Basmadjian v. Landry*, 54 USPQ2d 1617, 1619 (Bd. Pat. App. & Interf. 2000):

> the evidence [submitted under Rule 608(b)] may relate to patentability and need not be restricted to priority. Notice of Final Rule, Patent Interference Proceedings, 49 Fed. Reg. 84816 [*sic*, 48416], 48421 col. 3 (Dec. 12, 1984) *reprinted in* 1050 Off. Gaz. Pat. Office 385, 390 col. 3 (Jan. 29, 1985). For example, an applicant can establish that it is entitled to judgment *vis-a-vis* a patentee based on a *prima facie* showing of the unpatentability of the invention to the patentee under the first paragraph of 35 U.S.C. Section 112, *e.g.*, that the patentee's specification is not enabling.

Thus, a Rule 608(b) request presenting only *evidence of unpatentability* and an *explanation* why applicant is entitled to judgment over the patentee is sufficient basis for declaration of an interference.

X. THE PROPOSED INTERFERING SUBJECT MATTER OF PROPOSED COUNTS A AND B AND ALL CLAIMS OF THE '523 PATENT ARE UNPATENTABLE TO TRINCHIERI

Among the bases discussed above for denying Trinchieri benefit of the filing dates of the '945 and '817 applications, several apply with equal vigor to the Trinchieri '523 patent itself and serve as grounds for unpatentability to Trinchieri of all claims of the '523 patent.

A. All Claims Of The '523 Patent Are Unpatentable To Trinchieri For Failure To Disclose A Practical Utility For The Claimed Antibodies And How To Use Them

As discussed in Sections V.C and VI.C, the Trinchieri '945 and '817 applications fail to disclose any utility for any anti-IL-12 antibodies and no such utility is obvious, so these applications do not satisfy the utility requirement of Section 101 or the "how to use" requirement of Section 112, first paragraph. Moreover, the '523 patent provides

no additional disclosure respecting utility or "how to use." The only use disclosed in the '523 patent is identical to that of the '945 and '817 applications:

> Other uses for these novel polypeptides are in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

'523 patent, col. 10, ll. 25-28 (emphasis added). As for Trinchieri's '945 and '817 applications, there is no description of any *specific* diagnostic or therapeutic use for antibodies that react with NKSF.

Therefore, the entirety of argument and analysis found in Sections V.C and VI.C applies to the '523 patent. Consequently, the '523 patent does not disclose a practical utility for the antibodies of claims 1-7, as required by Section 101, and does not teach how to use those antibodies, as required by Section 112, first paragraph. Therefore, *all of claims 1-7* of the '523 patent are unpatentable to Trinchieri.

B. Claims 1, 2, 4 And 6 Of The '523 Patent Are Unpatentable To Trinchieri As Anticipated By The Stern *et al.* Publication

As shown above, the earliest possible effective filing date of the '523 patent for the subject matter of proposed count A and B is September 18, 1990. For the very same reasons, the earliest filing date to which the claims of the '523 patent are entitled is September 18, 1990. Briefly, the insufficiencies of the prior filed '945 and '817 applications noted in Sections V and VI apply to the '523 patent.

On September 12, 1990, the following publication became available to the public: Stern *et al.*, "Purification to homogeneity and partial characterization of cytotoxic maturation factor from human B-lymphoblastoid cells," Proc. Natl. Acad. Sci. USA 87: 6808-6812 (September 1, 1990) (attached as Exhibit N). As shown on the "received" stamp on the attached copy of the cover page of Volume 87, Issue 17 (September 1990) of the journal (attached as Exhibit O) from the Bio-Medical Library of the University of Minnesota, the issue was available at least as early as September 12, 1990.

At page 6809, the article discloses polyclonal and monoclonal antibodies to CLMF and the 40 kD subunit:

> **Anti-CLMF Antibodies**. A rat immunized with ~ 4 μg of partially purified human CLMF produced serum antibodies that neutralized CLMF bioactivity. Hybridoma cells secreting monoclonal antibodies to CLMF were produced by fusing NSO cells with splenocytes recovered from this rat. Antibodies were purified from ascites fluid by affinity chromatography on a GammaBind G-agarose column (Genex). Monoclonal anti-CLMF antibody 7B2 was found to

> be an IgG2a antibody that immunoprecipitated radiolabeled CLMF heterodimer and reacted with the 40-kDa subunit of CLMF, as demonstrated by immunoblot analysis (R.C. and T.T., unpublished data).

(Emphasis added). As expressly stated, "monoclonal antibody 7B2 . . . immunoprecipitated radiolabeled CLMF heterodimer and reacted with the 40-kDa subunit of CLMF."

The monoclonal antibody 7B2 of the above-quoted paragraph is the same antibody designated "7B2" in the captioned application (Benjamin Dec., ¶ 22). Further, Dr. Benjamin has stated that, based upon his knowledge that the amino acid sequence of the 40 kD subunit of the CLMF of the captioned application and the Stern *et al.* publication and the two NKSF proteins of the '523 patent, in his opinion *monoclonal antibody 7B2 would specifically react with the 40 kD subunit of all three proteins and specifically reacts with such CLMF and two NKSF proteins.*

Therefore, monoclonal antibody 7B2 reacts with NKSF, where that protein "is capable of inducing the synthesis of gamma interferon *in vitro* in human peripheral blood lympyhocytes (PBL) and is substantially free from association with other proteinaceous materials," as recited in claim 1 of the '523 patent. As previously noted, such activity is an inherent property of NKSF having the two subunits defined in claim 1 (Benjamin Dec., ¶ 10). Additionally, one of the NKSF sequences referred to by Dr. Benjamin, above, has (a) a first subunit having an apparent molecular weight of approximately 40 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of Fig. 1 from amino acids 23 to 328, and (b) a second subunit having an apparent molecular weight of approximately 30-35 kD under reducing conditions on SDS PAGE and comprising the amino acid sequence of Fig. 2 from amino acid 57 to 253. Thus, all limitations of claims 1, 2 and 6 of the '523 patent are met by monoclonal antibody 7B2.[14/]

Since monoclonal antibody 7B2 is within the scope of claims 1, 2, 4 and 6 of the '523 patent, the Stern *et al.* publication anticipates claims 1, 2, 4 and 6 of the '523 patent.

The Stern *et al.* publication is not prior art to Applicants' captioned application since the effective date of the captioned application for the subject matter of

---

[14/] Claim 4 adds the limitation that the antibody of claim 1 is a murine antibody. It is noted that the term "murine" encompasses rat species. See, *e.g.*, the definition provided in *The International Dictionary of Medicine and Biology*, Vol. II, 1986, John Wiley & Sons, Inc., p. 1816 (attached as Exhibit P), which states that the term "murine" is defined as "[o]f or pertaining to the rodent family Muridae, comprising rats and mice, as in *murine pneumonia*."

claims 33-44 is August 27, 1990 (see Section VII), which is before the Stern *et al.* publication became publicly available.

C. Claims 4 And 5, Which Are Directed To Murine And Human Antibodies, Are Unpatentable To Trinchieri For Lack Of Written Description

The '523 patent lacks written description of any "murine antibody" or "human antibody" since there is no mention of such subject matter in the patent. It was not until October 22, 1997 that claims filed by *preliminary amendment* in connection in the '240 application were added.

The '817 and '945 applications also fail to provide adequate support for how to make such *human* antibodies. For example, the '523 patent is completely silent as to how one of skill in the art could go about generating a human antibody which specifically reacts with *human* NKSF.

Additionally, methods for how to make a *human* antibody directed against a *human* antigen without having to resort to undue experimentation were beyond the state of the art at the time the '817 and '945 applications were filed (Benjamin Dec., ¶ 23). That is, significantly more than standard techniques would have been required to generate such human antibodies (Benjamin Dec., ¶ 23).

For these reasons, claims 4 and 5 of the '523 patent are unpatentable to Trinchieri for lack of written description and lack of enablement.

XI. COMPLIANCE WITH 35 U.S.C. § 135(b)

The provision of 35 U.S.C. § 135(b)(1) is not an impediment to declaration of an interference because the subject matter of claims 33-44 was claimed as early as September 22, 1999, which is within one year of issuance of the '523 patent on September 22, 1998.

For claims 33-38, see Applicants' Preliminary Amendment, dated September 22, 1999 in the captioned application, in which these claims were added. The only subsequent amendment to those claims was the addition of SEQ ID NOs. See Response To Office Action And Amendment, dated July 24, 2000.

New claims 39-44 have been added in this Response, which was filed more than one year after issuance of the '523 patent. However, long prior to issuance of the '523 patent, Applicants had claims directed to antibodies to CLMF and a full description of the complete amino acid sequences of both subunits of CLMF. See Gately application Serial No. 572,284, filed August 27, 1990, original claims 27-29, which read:

27. Antibodies in a substantially pure form to CLMF.

28. Antibodies to CLMF of Claim 27 wherein the antibodies are polyclonal.

29. Antibodies to CLMF of Claim 27 wherein the antibodies are monoclonal.

The amino acid sequence of both subunits of CLMF was presented in Figs. 25 and 26. These claims, which are directed to antibodies to CLMF, polyclonal antibodies to CLMF and monoclonal antibodies to CLMF, are directed to the same, or substantially the same, subject matter as claim 1 of the '523 patent and new claims 39 and 40 of the captioned application. Therefore, 35 U.S.C. § 135(b) is not a bar to claiming that subject matter.

XII. SPECIFIC COMMENTS ON THE EXAMINER'S POSITION

In the Office Action, dated February 22, 2002, the Examiner maintained the rejection of claims 33-38 under 35 U.S.C. § 102(e) over the Trinchieri '523 patent, contending that the '523 patent is entitled to an effective filing date of its '945 application, filed November 10, 1988, for the antibodies of its claims 1-7. Specifically, the Examiner stated that the '945 application:

> describes partial amino acid sequences of the protein and the biological activity of the protein, combined with the routine skill of one in the art at that time, a monoclonal antibody which reacts with the CLMF protein (also known as IL-12) was enabled and had utility (methods of diagnosis or therapeutic use).

Office Action, dated February 22, 2002, pp. 2-3. This statement is incorrect for the reasons presented earlier in this Response.

First, as noted in Section II.A.1, the Examiner required that the *complete* amino acid sequence of *both* subunits be recited in the antibody claims as a requirement for patentability. Necessarily, then, the interfering subject matter must be defined by those same sequences. Consequently, only if the earlier-filed application discloses the *complete* amino acid sequence for *both* subunits can it provide the basis for an effective filing date. As demonstrated in Sections V.A and VI.A, *neither* the '945 application nor the '817 application discloses the complete amino acid sequences for both subunits, so neither has a written description for the interfering subject matter and neither can serve as the basis for an effective filing date.

Second, while the Examiner is correct that the '945 application describes partial amino acid sequences of IL-12, the Examiner is incorrect in concluding (with no support provided) that such information would allow one to produce monoclonal antibodies to IL-12 using routine skill in the art. As demonstrated in Section V.D, there are six partial amino acid sequences disclosed in the '945 application, each from five to eight amino acids in length (Benjamin Dec., ¶ 18). It would have been difficult and uncertain as to whether one could elicit antibodies to a protein containing any of such peptides, even if the peptide were to be conjugated to a carrier protein (Benjamin Dec., ¶ 19). The quality and specificity of such antibodies would also be doubtful (Benjamin Dec., ¶ 19). Rather, a peptide of five to eight amino acids, generally, a peptide of at least approximately ten amino acids, would be used in generating antibodies (Benjamin Dec., ¶ 19). Thus, it would have been difficult and uncertain as to whether one could elicit antibodies specific for IL-12 using those peptides of the 30-35 kD subunit disclosed in the '945 application (Benjamin Dec., ¶ 19). See also, *e.g.*, Harlow & Lane (Exhibit M), which point out that, while synthetic peptides as short as six amino acids can be used to produce antibodies to a protein containing that sequence, antibody responses with such short sequences vary and standard methods teach that peptides of at least approximately ten amino acids should be used.

Third, the Examiner contends that the '945 application discloses a sufficient utility for antibodies to IL-12 in the disclosure that they may be used for "diagnostic and therapeutic uses." Applicants have shown in Sections V.C.1 and VI.C.1 that such nebulous, non-specific statement of utility is insufficient under the case law and the PTO's own Guidelines and Training Materials. Simply stated, "diagnostic and therapeutic use" does not provide a *specific* practical utility in the absence of a disclosure of a disease or disorder that may be diagnosed or therapeutically treated; neither the '945 application nor the '817 application disclose any such disease or disorder that can be diagnosed or treated with antibodies to IL-12. Consequently, the '523 patent is not entitled to the effective date of either the '945 or '817 application.

CONCLUSION

Applicants respectfully request declaration of an interference between the '523 patent and the captioned application for the subject matter of Applicants' proposed counts A and B. The proposed claim designations should be as follows:

Proposed Count A: Gately: claims 33-35, 37, 39-41 and 43

	Trinchieri:	claims 1, 2 and 4-6
Proposed Count B:	Gately:	claims 36, 38, 42 and 44
	Trinchieri:	claims 3 and 7

Applicants should be named senior party, since their effective filing date, August 27, 1990, as to both proposed counts A and B is prior to Trinchieri's effective filing date, September 18, 1990 (if Trinchieri is entitled to any benefit at all, given that the subject matter is unpatentable to Trinchieri).

Additionally, Applicants have shown above that (a) claims 1-7 of the '523 patent are unpatentable to Trinchieri because the patent lacks disclosure of any utility for the claimed subject matter and no utility is obvious, (b) claims 1-7 are unpatentable to Trinchieri because the patent fails to enable how to use the claimed subject matter, (c) claims 1, 2 and 6 are anticipated by the prior art, (d) claim 4 is obvious over the prior art and (e) claims 4 and 5 are unpatentable for lack of written description. Because none of the claims of the '523 patent are patentable to Trinchieri, Applicants' are *prima facie* entitled to judgment over the patent and an interference should be declared.

Respectfully submitted,

Dated: January 23, 2003

29,258
Thomas E. Friebel (Reg. No.)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036
(212) 790-9090

Attachments:

Exhibit A:	Copy of pending claims 33-44
Exhibit B:	Trinchieri *et al.*, Patent No. 5,811,523 ("'523 patent")
Exhibit C:	Trinchieri *et al.*, application Serial No. 07/307,817, filed February 7, 1989 ("'817 application")
Exhibit D:	Trinchieri *et al.*, application Serial No. 07/269,945, filed November 10, 1988 ("'945 application")
Exhibit E:	Gately *et al.*, application Serial No. 09/401,839, filed September 22, 1999 ("captioned application")
Exhibit F:	Gately *et al.*, application Serial No. 07/572,284, filed August 27, 1990

("'284 application")

Exhibit G: File history of Trinchieri *et al.* Patent No. 5,811,523

Exhibit H: Second Declaration of Dr. David H. Presky, filed July 24, 2000 ("Second Presky Declaration")

Exhibit I: D'Andrea *et al.*, 1992, J. Exp. Med. 176: 1387-1398 ("D'Andrea *et al.*")

Exhibit J: Chizzonite *et al.*, 1991, J. Immunol. 147: 1548-1556 ("Chizzonite *et al.*")

Exhibit K: Trinchieri *et al.*, Patent No. 6, 300,478 ("'478 patent")

Exhibit L: Request Under 37 C.F.R. §§ 1.607 and 1.608(a) For Interference With Patent No. 6,300,478, filed January 23, 2003, in Gately *et al.* application Serial No. 10/267,565 (without exhibits)

Exhibit M: *Antibodies: A Laboratory Manual*, 1988, (Harlow, E. & Lane, D., eds.) Cold Spring Harbor Laboratory, New York; p. 76 ("Harlow & Lane")

Exhibit N: Stern *et al.*, Proc. Natl. Acad. Sci. USA 87: 6808-12 (September 1990) ("Stern *et al.*")

Exhibit O: Cover page of Volume 87, Issue 17 (September 1990) of the Proc. Natl. Acad. Sci. USA from the Bio-Medical Library of the University of Minnesota

Exhibit P: *The International Dictionary of Medicine and Biology*, Vol. II 1986, John Wiley & Sons, Inc., p. 1816